THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Vol. 3, No. 4 OCT., 1956

JOURNAL DE LA SOCIÉTÉ CANADIENNE DES ANESTHÉSISTES

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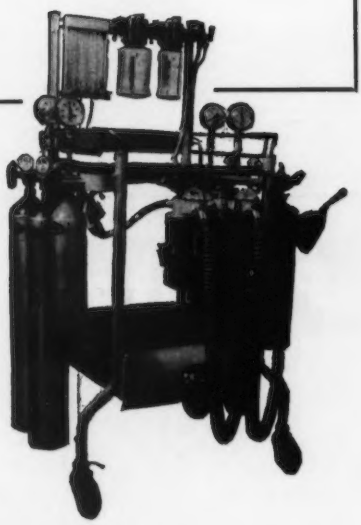

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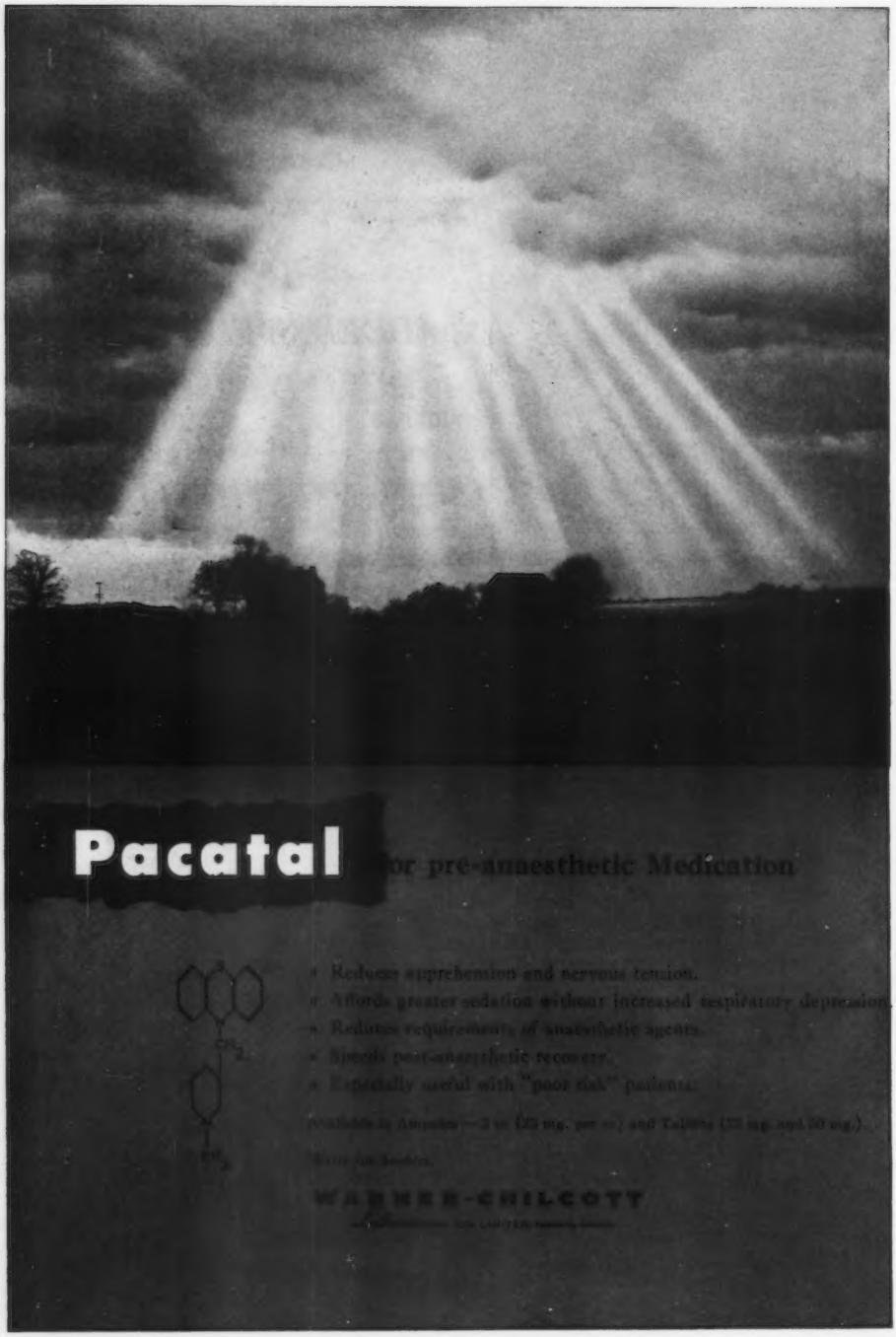
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1. Webster, C.W., C.M.A.J. Oct. 1953.

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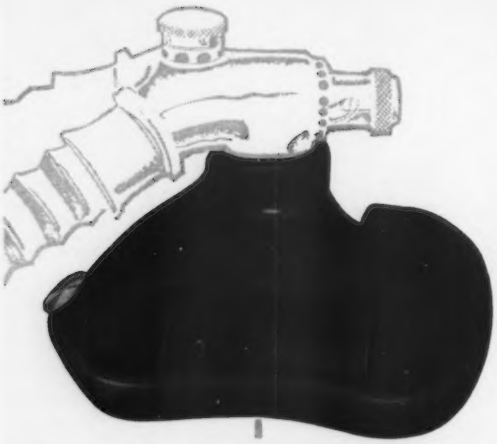

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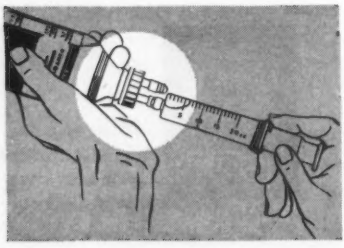

THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Combining

PROCEEDINGS OF THE CANADIAN ANAESTHETISTS' SOCIETY
CANADIAN ANAESTHETISTS' SOCIETY NEWS LETTER

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Printed and Published for
THE CANADIAN ANAESTHETISTS' SOCIETY, Incorporated
516 Medical Arts Building, Toronto 5, Canada

by

University of Toronto Press
University of Toronto
Toronto 5, Ontario, Canada

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Annual subscription $8.00

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EDITORIAL

New Drugs

Over twenty years ago Dr. Wesley Bourne, in an address to the Canadian Medical Association, said "The difficult position into which we are continually being brought concerning new drugs, as it accounts for, so it justifies, an attempt to estimate the usefulness of some of them" (1). These words are no less true, today, than they were two decades ago. The arresting difference, then and now, occurs in the greatly increased number of new drugs which must be examined in an attempt to estimate their usefulness to the armamentarium of the physician.

The approach of the physician to the investigation of a new drug must be objective in the extreme. We must realize that while many a new drug is the result of an honest search directed to the discovery of a hypothetical ideal in the field, and offered to the medical profession in good faith as something better than its predecessors, or even as embodying a new concept in medicine, there are many others which are produced on a purely commercial basis in the hope that they may be as good as some other substance used for the same purpose, and so become salable merchandise in the same market. A grave responsibility rests on investigators to distinguish in their reports, however subtly, the one from the other.

We need hardly emphasize in this Journal that clinical trials of a new drug should be preceded by extensive and confirmed knowledge of the pharmacological effects of the agent in several species of animal. Clinical trials following on this knowledge must be undertaken in the objective manner of a laboratory experiment, with accurate recording of all the relevant data. Analysis of recorded data must also be objective, studiously avoiding personal bias, pressure from representatives of manufacturers, that strange enthusiasm for the new drug which at times appears to overtake even the most seasoned investigator.

In reporting the results of the clinical evaluation of a new agent it is particularly important that objectivity should be a rigid rule. The enthusiast breeds the suspicion with which the scientifically educated mind reacts to the cultist, and so, through his very effort to persuade his audience beyond the logic of his evidence, he defeats his purpose. Thus a useful innovation may suffer from the enthusiasm of its advocates. Such advocates should be aware, too, that their advocacy has produced many fugitives from the printed word.

We are not suggesting that the investigator of a new drug should refrain from expressing an opinion of the usefulness of the substance under report; but let such an opinion be in the nature of a conclusion based on the evidence produced by his objective investigation of the drug, and suitably qualified by reference to limitations in the investigation, or equivocal data. The evidence being thus presented, the informed reader will be able to judge the value of the new drug to him in his daily effort to bring the best in current therapeutic agents to the relief of his patient.

Le Docteur Wesley Bourne, dans une causerie à la société médicale canadienne, il y a plus de 20 ans, s'exprimait ainsi: "En ce qui concerne les médicaments nouveaux, nous sommes toujours amenés dans une situation difficile, ce qui plaide

en faveur, justifie l'emploi; il faut essayer de mesurer l'utilité de certains d'entre eux". Cette affirmation n'est pas moins vraie aujourd'hui qu'elle ne l'était il y a deux décades. La principale différence, entre ce temps-là et aujourd'hui, réside dans le nombre considérablement accrû de médicaments nouveaux qu'il faut examiner dans le but d'évaluer leur utilité au médecin.

Pour faire l'évaluation d'un médicament nouveau, la façon de procéder du médecin doit être objective à l'extrême. Il nous faut réaliser que, si plusieurs médicaments nouveaux sont le résultat d'une recherche honnête orientée vers la découverte d'un idéal hypothétique dans ce domaine et offerts à la profession médicale en toute sincérité comme quelquechose de supérieur ou d'égal à ce qui existait au préalable et incorporant un nouveau concept médical, il en existe d'autres, par contre, qui sont produits sur une base uniquement commerciale dans l'espoir qu'ils puissent être aussi bons que certaines autres substances employées dans le même but et devenir ainsi concurrents des autres sur le marché. Une grave responsabilité échoit donc aux investigateurs: dans leurs rapports, il leur faut distinguer, avec subtilité toutefois, les uns des autres.

Il est à peine nécessaire de mentionner dans ce journal que les essais cliniques d'un médicament nouveau devraient être entrepris seulement avec une connaissance étendue et confirmée des effets pharmacologiques de l'agent en cause sur diverses espèces animales.

Avec cette connaissance, les essais cliniques doivent être entrepris avec la même objectivité qu'une expérience de laboratoire en tenant un compte précis de toutes les données. L'analyse de ces données doit également être objective; les tendances personnelles doivent être mises de coté aussi bien que la pression exercée par les représentants des manufacturiers; et il faudrait en dire autant de cet enthousiasme étrange pour le nouveau médicament, cet enthousiasme qui, parfois, semble s'emparer des plus tempérés des investigateurs.

En faisant part des résultats de l'évaluation clinique d'un nouveau médicament il devient tout à fait important que l'objectivité soit de rigueur. L'enthousiaste engendre le doute avec lequel l'esprit à tournure scientifique aborde le problème, et, ainsi, le même effort qu'il fait pour convaincre son auditoire de la logique de son évidence lui fait manquer son but. C'est ainsi qu'une innovation utile peut avoir à souffrir de l'enthousiasme de son avocat. Les avocats de cette catégorie devraient tenir compte également que de semblables plaidoyers ont contribué à chasser de la littérature plusieurs lecteurs.

Nous ne suggérons pas que l'investigateur d'un nouveau médicament doive s'abstenir d'exprimer une opinion sur l'utilité de la substance en cause, mais nous suggérons que cette opinion se présente comme la conclusion basée sur l'évidence produite par l'investigation objective du médicament; cette évidence doit également faire part et tenir compte des limites et de l'étendue de la recherche et des données douteuses. L'évidence ainsi présentée, le lecteur avisé pourra estimer la valeur que ce nouveau médicament peut avoir pour l'aider, dans son effort quotidien, à n'apporter que les meilleurs agents thérapeutiques pour le soulagement de son malade.

REFERENCES

1. Bourne, W. An Estimate of the Usefulness of Some of the Newer Anaesthetics in Practice. C.M.A.J. *31*: 44 (1934).

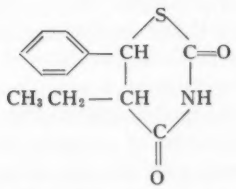
EVALUATION OF "DOLITRONE"*

GORDON M. WYANT, F.F.A.R.C.S., CHRISTOPHER J. KILDUFF, M.B., B.CH.,
JOHN E. MERRIMAN, M.D. and ALLEN B. DOBKIN, M.D.**

EARLY in 1954, Thompson, Smith, and Werner (1) first reported on some pharmacological properties of a new intravenous anaesthetic agent MRB-125, later to be named "Dolitrone."[1] This report was followed by three papers by Lundy in the same year (2, 3, 4). A further four publications by the same author in the following year (5, 6, 7, 8) reported on the clinical properties of the new agent with special emphasis on its general analgesic properties. Judging from these publications, Dolitrone seemed to be an agent worthy of thorough study. The work here reported relates to Dolitrone (*a*) as compared with the standard agent sodium thiopental (Pentothal®) under controlled conditions in volunteers, (*b*) as a general anaesthetic agent in clinical practice, and (*c*) as a general analgesic.

CHEMISTRY AND PHARMACOLOGY

Dolitrone is 5-ethyl-6-phenyl-m-thiazane-2,4-dione and has the following structural formula:



Thus Dolitrone is not a barbiturate. It is a white crystalline powder with a melting point of 159°C. It is insoluble in water but soluble in many organic solvents. The sodium salt is soluble in water; the pH of a 5 per cent solution is between 11.5 and 12 and that of a 2.5 per cent solution is 11.4. It is hygroscopic and unstable even in the anhydrous form. It must be dissolved in sterile water or normal saline since Dolitrone base will precipitate if the sodium salt is dissolved in glucose solution which is slightly acid. The 2.5 per cent solution so prepared is isotonic with human blood.

Pilot studies conducted in the laboratories of the Wm. S. Merrill Company and reported by Thompson, Smith, and Werner (1), indicated that in laboratory animals respiration was not seriously depressed by Dolitrone and laryngeal reflexes were markedly diminished. They also found that abdominal relaxation

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, at Mont Tremblant, P.Q., June 18, 1956.

**From the Departments of Anaesthesia and Medicine (Cardio-pulmonary Service) University of Saskatchewan College of Medicine & University Hospital, Saskatoon.

[1]Supplies of Dolitrone were made available through the courtesy of the Wm. S. Merrill Co. of Cincinnati, Ohio, U.S.A., who also generously supported this study by a grant-in-aid.

was good with doses which did not appreciably alter respiration and that the margin of safety of Dolitrone was greater than that of the barbiturates. With intravenous injection in rabbits, the $L.D._{50}$:M.H.D. (minimal hypnotic dose) ratio was 16 for Dolitrone as compared to 5 for sodium thiopental. In laboratory animals there was little or no cumulative effect with repeated doses and recovery was rapid following prolonged anaesthesia, in contradistinction to the barbiturates.

Duration of hypnosis in single 60 per cent $L.D._{50}$ doses was 53 minutes for Dolitrone and 20 minutes for sodium thiopental. With intravenous injection in rabbits the acute $L.D._{50}$ for Dolitrone was approximately 3 times that of sodium thiopental. Minimal hypnotic doses for both agents were similar. Blood pressure in dogs receiving repeated rapid intravenous injections of Dolitrone was not appreciably altered until the stage of respiratory arrest was reached. The heart rate in dogs was not affected by the prolonged administration of Dolitrone and no changes of blood picture, weight, gross and microscopic examination of vital organs were observed after dogs had been maintained in deep surgical anaesthesia with Dolitrone for two 90-minute periods. Seldon (9) states that the capillaries in the rabbit's ear, as seen with the aid of a Clarke window, are smaller when Dolitrone is used than they are with ether, cyclopropane, ethylene, or sodium thiopental, and resemble somewhat the state of the capillaries under nitrous oxide-oxygen anaesthesia. Cotten and Bay (10) found that in dogs both Dolitrone and sodium thiopental had only limited effects on blood pressure, force of ventricular contraction, and the electrocardiogram, but both produced marked tachycardia in equivalent doses. They also stated that, following Dolitrone, fewer epinephrine-induced arrhythmias were found than after sodium thiopental. In contradistinction to Thompson, Smith, and Werner they found that with equivalent anaesthetic doses the duration of anaesthesia was approximately identical for both drugs. The respiratory rate was not seriously reduced in non-premedicated animals, but following pre-treatment with morphine, Dolitrone was well tolerated whereas sodium thiopental frequently produced fatal respiratory arrest. In 20 per cent of dogs, Cotten and Bay observed intense excitement during emergence, which was not seen after thiopental.

Comparative Study in Volunteers

Healthy volunteers, 9 males and 1 female, were selected and on each two studies were carried out at an interval of one week. During the first sitting sodium thiopental was studied and on the second sitting Dolitrone. The volunteers reported to the Department of Anaesthesia at 8:00 A.M. having had no breakfast. They were admitted to the recovery room where their height and weight were recorded. They were then made to rest for approximately one hour. No pre-anaesthetic medication whatsoever was given, except to volunteer 8 who was unable to hold the mouthpiece without gagging. He received meperidine (Demerol®) 50 mg. intravenously on each occasion.

Blood pressure, pulse, and respiration were recorded. An arterial puncture was done using a No. 20 gauge Riley needle which was left *in situ* throughout the experiment. By means of a mouthpiece, nose clip, and three-way respiratory

valve, expired air was collected in a Tissot spirometer. Serial one-minute collections of expired air were made, usually four or five, until a steady state had been obtained as judged by the constancy of the minute ventilation volume. These collection periods also allowed for an adequate washout of the apparatus dead space. As soon as a steady state had been reached the kymograph on the Tissot spirometer was started to measure respiratory frequency and a three-minute collection of expired air was obtained. During the middle of this collection a sample of arterial blood was drawn anaerobically into oiled and heparinized syringes. A venous puncture was then carried out with a large bore needle and a Gordh needle mount was attached and securely fastened to the arm.

Samples were analysed as follows. The tidal volume was calculated from the three-minute expired volume divided by the total number of respirations. All volumes are corrected to B.T.P.S. (body temperature, pressure and saturated). A representative sample of the expired air was stored in a mercury reservoir and subsequently analysed using the micro-Scholander apparatus for carbon dioxide and oxygen contents. In two experiments the expired air was analysed using a pulmo-analyser for carbon dioxide and a Beckman analyser for oxygen. These two analysers had previously been calibrated against the micro-Scholander. Gas respiratory quotients and oxygen consumption were then calculated using the standard formulae (11).

The arterial blood was analysed for its oxygen and carbon dioxide content using the technique of Van Slyke and Neill (12) and the oxygen capacity was determined after equilibrium of the blood with room air in a tonometer for 15 minutes. The percentage of oxygen saturation was corrected for dissolved oxygen.

At the first sitting anaesthesia was induced with sodium thiopental 2.5 per cent using a double sleep dose. Immediately thereafter succinylcholine 20 or 30 mg. was given. The larynx was exposed, and both cords and trachea were sprayed with 2 ml. of 1 per cent tetracaine (Pontocaine®) followed by insertion of a cuffed No. 10 Magill endotracheal tube lubricated with cyclomethycaine (Surfacaine®) jelly 0.75 per cent. The same endotracheal tube was used in all experiments in order to keep resistance to respiration and dead space changes constant. If, following intubation, there was apnoea or inadequate respiratory excursion, mouth-to-tube breathing was carried out. Oxygen was not used in order not to interfere with blood oxygenation studies. A period of 10-15 minutes was permitted to elapse until it was certain that all residual effects of the relaxant had worn off. During this time and thereafter, fractional doses of sodium thiopental 1 per cent were administered by syringe to maintain the patient at a steady depth of anaesthesia as judged by the electroencephalogram. The level of anaesthesia chosen for each patient was the lightest which would permit retention of the endotracheal tube without bucking and straining; usually mid-second electroencephalographic level was required. If necessary, somewhat deeper levels were maintained. At the end of the waiting period respiratory studies were repeated; expiratory air and arterial blood samples were taken again for gas analyses. Thereafter anaesthesia was maintained for exactly 30 minutes at a steady level by means of fractional supplements of sodium thiopental 1 per cent. The endotracheal tube remained connected to the non-

rebreathing valve throughout the experiment in order not to alter the dead space. All readings and blood samples were repeated at the end of the 30 minutes. While this study was in progress the patient's reaction to pain was determined by inserting a towel clip through the skin to one side of the umbilicus and the response was noted. Blood pressure and pulse were recorded from time to time and the electrocardiogram was continuously observed and recorded.

At the conclusion of the experiment the subjects were extubated and observed in the recovery room where their response to verbal stimuli was noted. The point at which they opened their eyes on command was considered the end point of the experiment.

The same technique was used the following week for the Dolitrone experiment with the exception that after initial pilot runs it was found that maintenance of anaesthesia with 1 per cent fractional doses of Dolitrone was frequently impossible. Therefore, after induction with Dolitrone 2.5 per cent, anaesthesia was maintained with Dolitrone 2 per cent. Maintenance of anaesthesia at the same level as that of sodium thiopental the previous week was attempted. In many instances this was too light and the endotracheal tube was not tolerated; anaesthesia was then deepened to the lightest satisfactory level.

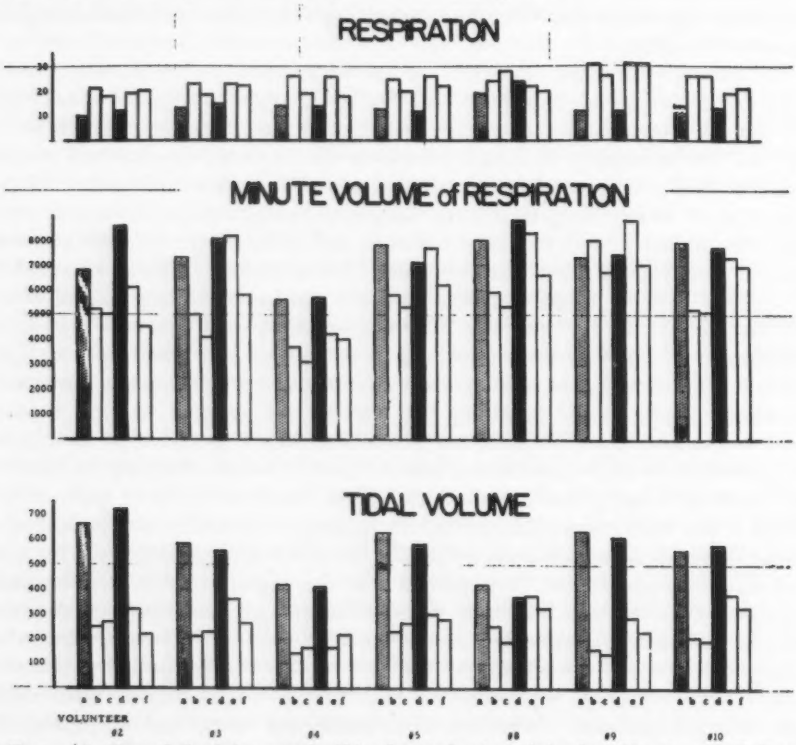


FIGURE 1. Pentothal: (*a*) control, (*b*) after induction, (*c*) after 30 minutes. Dolitrone: (*d*) control, (*e*) after induction, (*f*) after 30 minutes.

After the necessary trial runs to test the experimental set-up, 9 volunteers were subjected to the experiment. With one of them smooth maintenance with Dolitrone proved impossible even with the most rapid possible rate of injection of the 2 per cent solution. One volunteer did not return for the second experiment, leaving 7 valid pairs of results for comparison.

Results

Tidal volume, respiratory rate and minute volume. Figure 1 shows the findings for each volunteer. It is evident from the chart that neither tidal nor minute volume could in all cases be reproduced exactly in the control study of the second sitting. Where discrepancies between the two controls arise in the tidal volume these are exaggerated for the minute volume as one might expect. It is evident, however, that by and large respiratory changes during Dolitrone anaesthesia are not as marked as with sodium thiopental.

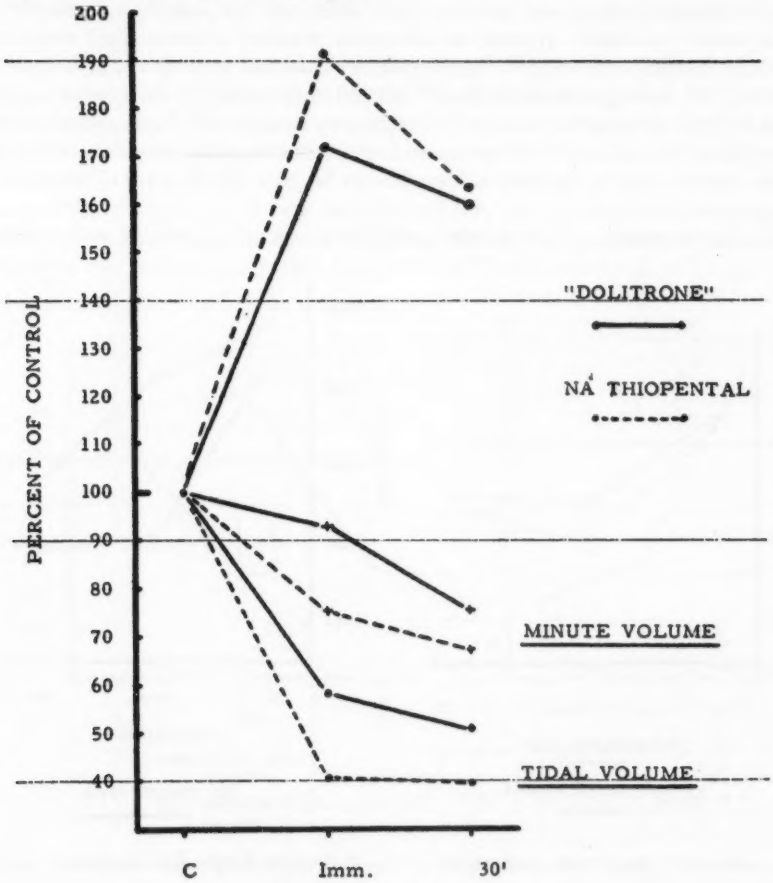


Figure 2. Respiratory rate.

In order to demonstrate this better, averages for all seven studies were determined and were related to pre-anaesthetic control values arbitrarily set at 100 per cent. This chart (Fig. 2) shows that the *tidal volume* with sodium thiopental falls after induction to 40 per cent of normal and tends to remain at this level at the end of 30 minutes, whereas with Dolitrone the initial fall is to only 58 per cent of normal; at the end of 30 minutes, however, a further decrease in tidal volume with Dolitrone takes place. In the post-induction measurements the *respiratory rate* with sodium thiopental rises sharply to over 190 per cent of normal whereas with Dolitrone it only rises to 170 per cent. However, at the end of the 30-minute period, both agents show a decline, more pronounced with sodium thiopental than with Dolitrone. The resultant *minute volume* shows a tendency similar to the tidal volume, in that the initial depression of minute volume with sodium thiopental is markedly more pronounced than that with Dolitrone, but Dolitrone tends to approximate the sodium thiopental values at the 30-minute reading.

Respiratory quotient. In order to determine whether a steady state existed at the time samples were drawn, the respiratory quotient was determined for each reading and averages were plotted. Figure 3 shows that at the control experiment and the 30-minute reading the respiratory quotient for both agents is very close. There is a somewhat larger spread at the reading after induction of anaesthesia, but it is not a significant difference as far as a steady state of the patient is concerned.

Alveolar ventilation. The alveolar ventilation was calculated for each reading

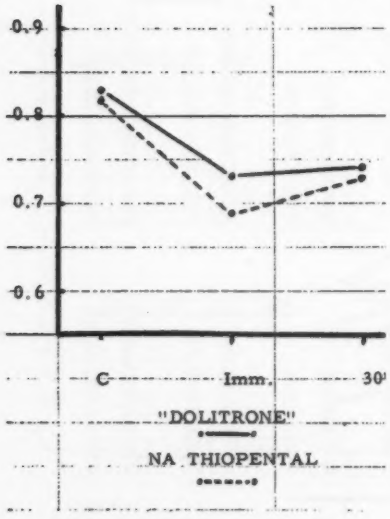


FIGURE 3. Respiratory quotient.

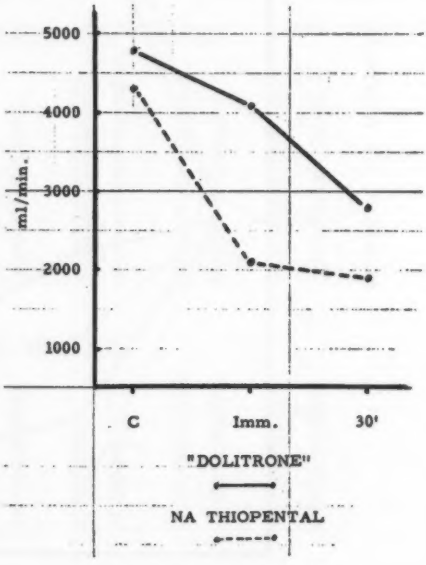


FIGURE 4. Alveolar ventilation.

in every volunteer and average values were plotted (Fig. 4). Calculations of alveolar ventilation were made on the basis of the formula

$$V_A = (V_T - V_{DS})\ frequency$$

where "V_T" represents tidal volume and "V_{DS}" dead space; 75 ml. was determined for the non-rebreathing valve, 10 ml. for the endotracheal tube, and 10 ml. for the mouthpiece. An average value of 120 ml. anatomical dead space was postulated. Thirty ml. was set for the anatomical dead space below the distal end of the endotracheal tube. No adjustment was made for the presumed diminished dead space in the one female volunteer (No. 4) since allowance would also have had to be made for the presumably larger dead space in one or two of the volunteers with a larger body surface area. In the absence of direct determinations of dead space this would have been guess work. It was therefore assumed that the dead space figures used constituted a fair average. The average alveolar ventilation as plotted on the table approximates closely the minute volume tracings (Fig. 2).

Oxygen consumption. Estimates of the average oxygen consumption per body surface area (Fig. 5) show that a similar relationship obtains as in the previous tracings. Oxygen consumption in millilitres per minute remains fairly steady for Dolitrone when the post-induction is compared with the control reading, but falls sharply towards the end of the 30-minute period, whereas with sodium thiopental the initial fall is very marked and the decline of oxygen consumption in the second period is less marked. Thus the oxygen consumption values for Dolitrone and sodium thiopental at the end of the 30-minute period again tend

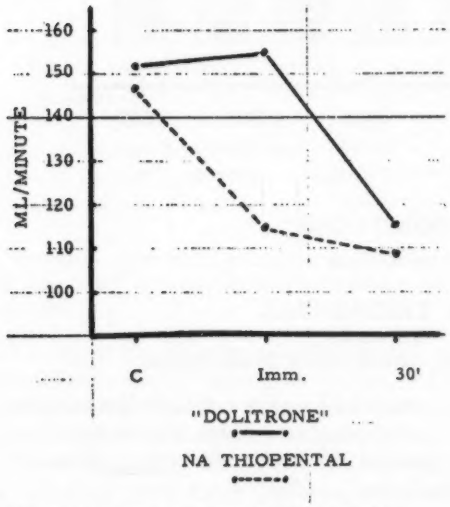


FIGURE 5. Oxygen consumption/body surface.

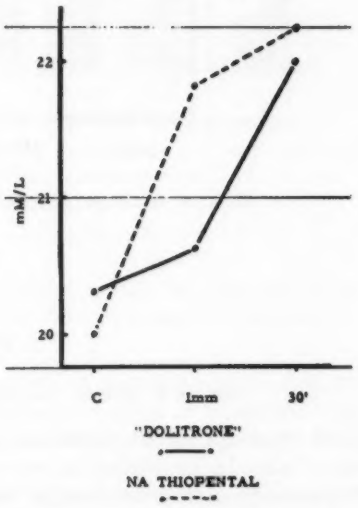


FIGURE 6. Arterial carbon dioxide content.

to approximate each other. The difference between them at the end of the 30-minute period is almost identical to their difference in the control determinations.

Arterial carbon dioxide content. Carbon dioxide content in arterial blood (Fig. 6) shows the tendency one might expect from previous tracings, namely that the increase in arterial carbon dioxide for Dolitrone is less marked in the first than in the second period, whereas with sodium thiopental it rises sharply in the first period and more gradually in the second period. Again the values at the end of the 30-minute period seem to come closer.

Figure 7 is derived from the two preceding tracings by plotting alveolar ventilation against arterial carbon dioxide content. In comparing Figures 5 and 6,

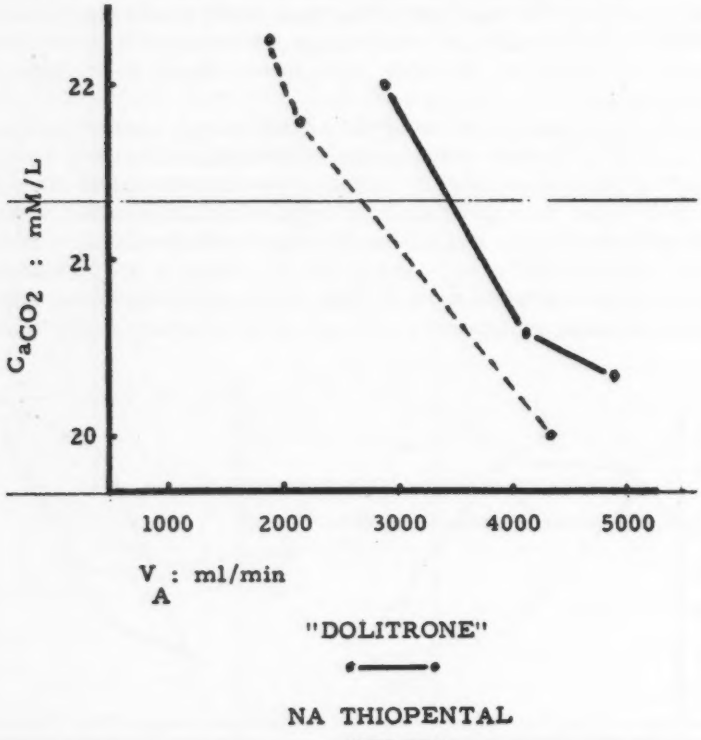


FIGURE 7. Alveolar ventilation: Arterial carbon dioxide content.

which represent almost picture images, one would expect a straight-line relationship of alveolar ventilation to arterial carbon dioxide content. This is indeed so. The tracings are almost straight and parallel. The slight deviations which are seen are within the limits of experimental error.

Total amounts of anaesthetic. Since anaesthesia was of equal duration for each volunteer at both sittings, the amounts of sodium thiopental and of Doli-

trone both for induction and for maintenance of anaesthesia are compared by means of a graph (Fig. 8). All preoperative factors were equal for each volunteer, as was also the dose of relaxant required for endotracheal intubation. The graph shows that frequently, but not invariably, more Dolitrone than sodium thiopental is required for induction. Without exception more Dolitrone is required for maintenance of anaesthesia than sodium thiopental and only in one case

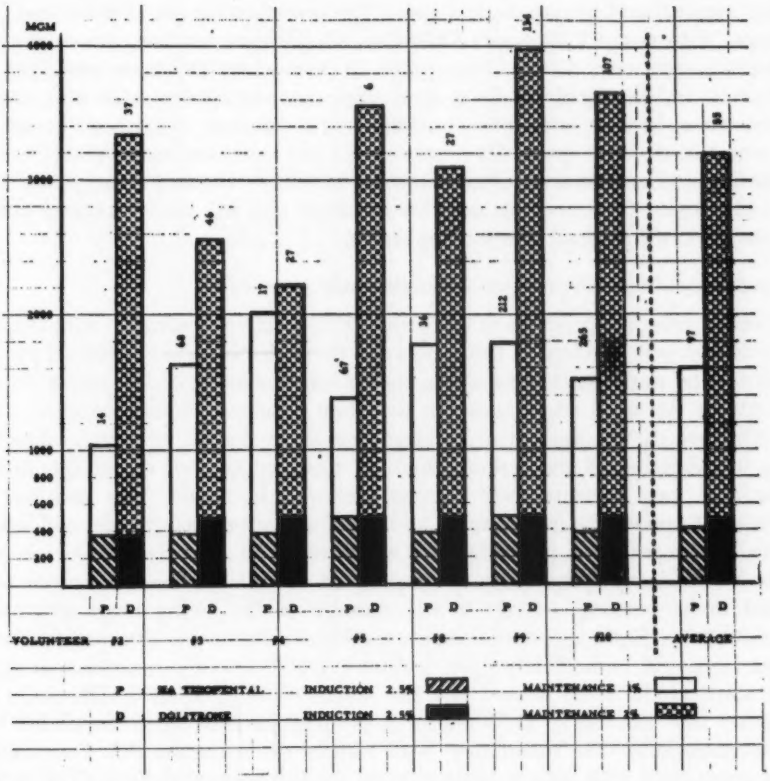


FIGURE 8. Amount of anaesthetic and postanaesthetic reaction time. Bars represent amount of anaesthetic for induction and maintenance; numbers above bars denote reaction time in minutes.

(No. 4) is the difference insignificant. The graph of averages reveals that for induction a slightly increased amount of Dolitrone is needed as compared with sodium thiopental. For maintenance the dose of Dolitrone in milligrams is more than double that of sodium thiopental.

Awakening time. This has been entered on Fig. 8 above each bar as number of minutes. Only twice (volunteers 2 and 4) did the individual react to the spoken word earlier after sodium thiopental than after Dolitrone. However, in volunteer 2 the total dose of Dolitrone was more than three times that of sodium

thiopental. On the average, volunteers after sodium thiopental reacted to the spoken word after 97 minutes from the end of anaesthesia whereas after double the amount of Dolitrone they reacted within 55 minutes.

Clinical Study

Armed with the information gained from our studies on volunteers, we took Dolitrone into the . operating room and used it in actual clinical anaesthesia on minor surgical and gynaecological cases. The investigation was divided into four groups. With group I (9 cases) Dolitrone, 2.5 per cent solution, was used as an induction agent only. Group II comprises 10 cases where Dolitrone was given for induction and in fractional doses as a supplement to nitrous oxide and oxygen maintenance because with nitrous oxide alone satisfactory anaesthesia could not be maintained. With group III Dolitrone 2.5 per cent was used throughout for induction and maintenance of anaesthesia (15 cases). Group IV comprises cases in which again Dolitrone was used for induction and full maintenance of anaesthesia but as a 2 per cent solution (14 cases).

Group I: Dolitrone 2.5 per cent–Induction only (9 cases)

Table I lists the nine cases in this group. Preoperative medication with meperidine 50 mg. was standard in this group and the interval elapsing between premedication and start of anaesthesia was held as constant as is possible under clinical conditions. As in all other cases the induction dose was double the sleep dose. In other words, the amount of Dolitrone necessary for the patient to close the eyes was determined and a similar amount was then injected moderately fast.

In only two patients short apnoea followed induction. The presence or absence of apnoea did not seem to be related to the patient's weight and height or to the closeness of premedication to induction of anaesthesia. Only in one case was endotracheal intubation carried out and in this case the cords were found to be reacting actively to the stimulus of the laryngoscope and endotracheal tube. Eight inductions were considered satisfactory. One patient developed hiccoughs immediately upon induction and before the maintenance agent was started. The same patient also had some retching, but it is difficult to say whether this was due to Dolitrone or to the maintenance agent. In all but two cases anaesthesia was maintained with nitrous oxide–oxygen 8:2. One patient was maintained with nitrous oxide–oxygen 7:2 and trichlorethylene (Trilene®), and one patient was maintained with cyclopropane. In one case there was slight movement during the surgical procedure, not sufficient to warrant supplemental doses of Dolitrone.

Mild phlebitis, defined as a tender, hard vein at the site of injection without spontaneous pains or reddening was encountered once on the first postoperative day.

Group II: Dolitrone 2.5 per cent–Induction and supplementation of nitrous oxide (10 cases)

In all these cases nitrous oxide anaesthesia was supplemented by Dolitrone because nitrous oxide by itself proved insufficient to control the patient ade-

TABLE 1

Induction Only
(Dolitrone 2.5 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication: Meperidine (mgm)	Time before induction (min)	Dose (mgm)	Maintenance agent	Total duration of anaesthesia (min)	Apnoea	Intubated	Phlebitis	
1	E.U.A.; D & C; Biopsy cervix	125	60	50	70	500	N_2O (8:2)	14	15″	No	No	Satisfactory
2	Oesophagoscopy	157	68	50	84	425	N_2O (7:2)TCE	9	No	Reactive	No	Satisfactory
3	E.U.A.; D & C	133	64	50	66	450	N_2O (7:2)	24	No	No	No	Satisfactory
4	E.U.A.	144	64	50	75	400	N_2O (8:2)	13	No	No	No	Satisfactory
5	E.U.A.; D & C	126	70	50	99	500	N_2O (8:2)	14	30″	No	No	Hiccough; retching
6	Uterine Curettage	134	66	50	93	500	N_2O (8:2)	15	No	No	No	Moving
7	Cystoscopy	168	69	50	116	500	N_2O (8:2)	12	No	No	No	Satisfactory
8	E.U.A.; Uterine curettage	115	62	50		500	N_2O (8:2)	14	No	No	+	Satisfactory
9	Biopsy vagina & cervix; Dilatation; E.U.A.	126	63	50	125	500	Cyclo	28	No	No	No	Satisfactory

TABLE II

Induction and Supplement to General Anaesthesia
(Dolitrone 2.5 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication: Meperidine i.m. (mgm)	Time before induction (min)	Dolitrone induction dose (mgm)	Maintenance agent	Dolitrone supplemental dose (mgm)	Supplemental started after induction (min)	Duration of Supplemental (min)	Total duration of anaesthesia (min)	Relaxation	Apnoea	Analgesia	Eyes open after Anaesthesia (min)	Phlebitis	
1	Hymenectomy, E.U.A.; D & C Biopsy cervix	121	66	25	50	400	N_2O (6:2)	225	5	5	27	S'Chol	No	?	?	No	Leg movements controlled with Dol. Hypotension 30 mm Hg with supplements.
2	E.U.A.; D & C	128	64	25	92	400	N_2O (8:2)	100	14	2	19	S'Chol	5"	?	4	No	Swallowing controlled by Dol. Carpo-pedal spasm.
3	E.U.A.; D & C	100	62	25	75	450	N_2O (8:2)	175	4	6	15	+	No	?	11	+	Movements controlled by Dol.
4	E.U.A.; D & C	166	64½	50	65	450	N_2O (8:2)	50	12	S.D.	17	S'Chol	No	?	13	No	Crowing controlled by Dol.
5	E.U.A.; D & C	136	60	50	85	450	N_2O (8:2)	25	8	S.D.	15	+	No	+	5	No	Coughing controlled by Dol.
6	D & C	133	65	50	67	450	N_2O (8:2)	50	16	S.D.	24	++	No	+	3	No	Movement controlled by Dol.
7	E.U.A.; D & C	126	61	50	113	400	N_2O (8:2)	50	11	S.D.	24	+++	No	No	1½	+	Slight movement hands. Controlled by Dol.
8	Biopsy cervix E.U.A.; D & C;	116	62½	25	110	375	N_2O (8:2)	100	1	S.D.	15	+	No	?	1	+	Movement limbs. Controlled by Dol.
9	E.U.A.; D & C;	115	63	25	85	400	N_2O (8:2)	100	12	2	19	++	No	1'	3	No	Swallowing and laryngo-spasm. Controlled by Dol.
10	E.U.A.; D & C Biopsy cervix	135	67	50	85	450	N_2O (8:2)	225	6	12	23	S'Chol	No	?4'	3	No	Repeated movement. Controlled by fract. Dol.

quately. This was because of either movements which proved disturbing to the surgeon, or coughing, crowing, laryngeal stridor, or swallowing (Table II). In one case hypotension of 30 mm. Hg occurred with the supplement and one other patient developed carpo-pedal spasm. This patient was shown to have a borderline blood calcium level and so carpo-pedal spasm cannot be attributed to Dolitrone. Apnoea of five seconds followed induction in only one case. Relaxation for the procedure, which was usually a pelvic examination under anaesthesia with or without dilatation and curettage, was excellent in one instance, good in two cases, fair in three cases. There was no relaxation in four instances and succinylcholine was needed. The total time from the end of anaesthesia until the patient responded to verbal stimuli was unpredictable, varying between one and thirteen minutes and being unrelated apparently to the total dose of Dolitrone, body surface area, or premedication. However, there seemed to be a relationship between the amount of preoperative medication and the necessity for Dolitrone supplementation since five patients in this series only received meperidine 25 mg. Residual analgesia was tested in five of these patients. It was absent in one, definitely present in three, and possibly present in one patient. However, since these patients had received nitrous oxide and were not always entirely co-operative when tested immediately at the end of operation, it is difficult to be certain whether analgesia did exist and the actual duration of it. None of the patients in this group were intubated. Two developed mild phlebitis.

Group III: Dolitrone 2.5 per cent—Induction and full maintenance (15 cases)

After induction with double the sleep dose of Dolitrone, anaesthesia was maintained by intermittent fractional supplements of Dolitrone 2.5 per cent, given as required (Table III). All patients received oxygen by mask. Nine patients in this series required no further anaesthesia and in seven the anaesthetic obtained was entirely satisfactory. One had some slight movements which required no further anaesthetic. Hypertension with bradycardia developed in one patient. Relaxation was excellent in two of these patients, good in six, and fair in one; none required a relaxant. Apnoea after induction was not seen and terminal analgesia was either absent or doubtful. There was a marked difference in the recovery time. This varied between 6 and 34 minutes, and again was entirely unrelated to total dose, body surface area, or preoperative medication. The disturbing feature in this group was the high incidence of severe phlebitis (3 cases) and marked phlebitis (1 case) defined as hardening and reddening of the vein along the arm with spontaneous pain and induration of the arm, requiring special treatment.

In the same group are six cases in which induction and maintenance with Dolitrone proved unsatisfactory or even impossible and a change had to be made to other agents. In one case sodium thiopental was substituted and all other cases were managed either with nitrous oxide–oxygen or nitrous oxide–oxygen–trichlorethylene. Muscle relaxation in these patients was much less satisfactory than in those maintained solely on Dolitrone. Apnoea during induction was again not seen nor was there evidence of postoperative analgesia. The rate of severe phlebitis was very high (5 patients out of 6). One of the patients actually

TABLE III

A. Induction and Full Maintenance
(Dolitrone 2.5 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication: Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of maintenance (min)	Oxygen L/min	Start anaesthesia to end operation (min)	Relaxation	Apnoea	Analgesia	Eyes open after last Dolitrone (min)	Phlebitis	
1	E.U.A.; D & C	155	64	50	79	400	300	1½	8	4	10	++	No	No	11	++	Satisfactory
2	E.U.A.; D & C Biopsy cervix	168	66	50	75	450	350	1	6	4	13	+	No	?2′	6	No	Satisfactory
3	E.U.A.; D & C; Manip. retrovert. uterus	140½	67	50	76	400	475	1	7	4	12	++	No	No	16	No	Satisfactory
4	E.U.A.; D & C	135	64	25	70	400	325	1	9	4	10	++	No	?3′	5	+++	Satisfactory
5	E.U.A.; D & C	175½	65	25	75	400	600	½	9½	4	16	+++	No	No	16	No	Movements not entirely controlled
6	E.U.A.; D & C; Manip. retrovert. uterus	120	64	25	77	400	375	1	7	4	13	++	No	?	34	No	Satisfactory
7	Cystoscopy; E.U.A.; D & C; Biopsy cervix	152	67	50	105	400	350	1	12	4	18	++	No	No	18	+++	Satisfactory
8	E.U.A.; D & C	135	60	25	155	400	375	2	13	8	17	++	No	No	12	+++	Hypertension and bradycardia
9	E.U.A.; D & C	112	65	50	108	500	500	1	9½	4	13½	+++	No	+	27	No	Movements during dilat. controlled by Dol.

TABLE III (*cont'd*)

B. Induction and Maintenance Requiring Change to Other Agents

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication: Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of maintenance (min)	Other agent	Duration of anaesthesia (min)	Relaxation	Apnoea	Analgesia	Eyes open after anaesthesia (min)	Phlebitis	Reason for other Agent
1	Laryngoscopy; biopsy vocal cords	179	71½	50	73	450	425	2	21	Pent. 0.5 Gm	21	DMC	No	?	?	+++	Cords too reactive.
2	E.U.A.; D & C	129	61	25	82	400	600	1	5	N_2O-TCE-O_2	17	No	No			No	Movements not controllable by Dol. 1 Gm.
3	E.U.A.; Aspir. Cul-de-sac; D & C	162	64	25	35(iv)	400	475	1	4	N_2O-O_2 (+Dol)	24	++	No	No	14	+++	Movements not controlled by Dol. Another 75 mgm. Dol. with N_2O to control crowing.
4	E.U.A.; D & C; Biopsy cervix	138	62	25	151	400	600	1	19	N_2O-O_2	28	+	No	No	8	+++	Slight movements throughout. N_2O after Dol. 1 Gm.
5	E.U.A.; D & C	111	65	25	180	500	400	2	4	N_2O-TCE-O_2	19	No	No	No		+++	Severe movements not controlled with Dol.
6	E.U.A.; D & C; Manip. Retrov. uterus	145	65	50	130	500	500	2	5	N_2O-TCE-O_2	20	++	No		2	+++	Severe movements not controlled with Dol.

required prolonged physiotherapy treatment in order to correct the severe inflammatory process in her arm. The vocal cords of the patient for laryngoscopy and biopsy of cords were too reactive. In others severe movements of the patient could not be controlled with Dolitrone. These movements were both spontaneous and on stimulation, manifesting themselves by flexion and rigidity of arms and legs to an extreme degree. One interesting feature was that in all perineal operations the perineum did not seem to withdraw from stimulation but remained immobile despite movement of the extremities. Again, a marked variation was seen in the reaction time at the end of anaesthesia, similar to that in the previous group.

Group IV: Dolitrone 2 per cent–Induction and maintenance (14 cases)

The change to 2 per cent solution was made in order to prevent if possible the high incidence of phlebitis which had been encountered in the group induced and maintained with Dolitrone 2.5 per cent. In eleven of these fourteen patients Dolitrone alone was used satisfactorily (Table IV). No marked or severe phlebitis occurred and only four cases of mild phlebitis were noted. The 2 per cent solution of Dolitrone seemed to have the disadvantage of even less potency, with a larger number of patients showing either mild movements, phonation, moaning, sighing, or swallowing. These did not significantly disturb the surgeon and therefore no further supplementation was required. One patient had very violent movements although a total of 1.5 Gm. Dolitrone was given in order to determine whether increased amounts of the drug might not control these movements. This was not found to be so. It is interesting in this connection to compare cases 8 and 9. Both patients were of approximately the same height and weight, and received the same premedication approximately the same time before induction of anaesthesia. The double sleep dose in both patients was equal, yet one of them required only 200 mg. supplemental Dolitrone for a six-minute procedure whereas the other required 1100 mg. for an eleven-minute procedure. In the patient who received a total of 600 mg. Dolitrone, anaesthesia was entirely satisfactory, whereas the patient with 1500 mg. moved violently and could not be controlled by this large dose. Yet despite the large discrepancy in the dosage both patients reacted to the spoken word within 23 minutes of the end of anaesthesia. Again there was no apnoea in this group. Analgesia was conspicuous by its absence. Mild phlebitis occurred once.

In three further patients violent uncontrollable movements necessitated a change to nitrous oxide–oxygen–trichlorethylene after 1 Gm. of Dolitrone had been administered and in no way controlled the movements. They were so severe that the surgeon was unable to proceed with the operation. Despite the identical total amount of Dolitrone of 1 Gm. each and identical nitrous oxide–oxygen–trichlorethylene supplementation, the reaction time varied between 17 and 41 minutes.

Discussion

Tidal volume, minute volume, alveolar ventilation, and arterial carbon dioxide content all seem to indicate that under our standard experimental conditions Dolitrone depresses respiratory functions to a less degree than does sodium

TABLE IV

A. Induction and Full Maintenance
(Dolitrone 2 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication: Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of maintenance (min)	Oxygen L/min	Start anaesthesia to end operation (min)	Relaxation	Apnoea	Analgesia	Eyes open after last dose Dol. (min)	Phlebitis	
1	E.U.A.; D & C; Biopsy cervix	109	63	50	79	400	240	1	9	4	17	++	No	No	25	No	Progressive fall systolic blood pressure
2	E.U.A.; D & C	120	64	50	86	480	520	1	10	4	13	++	No	No	34	No	Movements not entirely controlled
3	E.U.A.; D & C; Biopsy cervix	172	63	50	86	400	300	2	6	5	12	++	No	No	5	No	Phonation; slight movement; moaning
4	E.U.A.; D & C; Polypectomy; Biopsy cervix	121	63½	50	150	400	200	1	11	4	17	++	No	No	23	+	Sighing; swallowing. Slight movements towards end
5	E.U.A.; D & C; Biopsy cervix	113	65	25	118	360	160	1	8	4	12	++	No	No	39	+	Satisfactory
6	E.U.A.; D & C	157	61	50	154	320	360	1	12	4	12	+	No	?	4	No	Swallowing; moaning; slight movements
7	E.U.A.; D & C; Biopsy cervix	136	60	50	82	360	120	1½	3½	4	9	+++	No	No	15	+	Very slight movements controlled with Dol.
8	D & C; E.U.A.	138	64	50	84	400	1100	1	11	4	20	++	No	No	23	No	Violent movements. Not controlled by 1.5 Gm. Dol.
9	D & C; Biopsy cervix; E.U.A.	129	65	50	88	400	200	1	6	4	11	+++	No	No	23	+	Satisfactory
10	E.U.A.; D & C	133	64	50	80	400	320	1	9	8	16	+++	No	No	29	No	Mild movement once; controlled by Dol.
11	Cystoscopy; Retrograde pyelogram; E.U.A.; Biopsy cevrix; D & C	133	64	50	96	400	280	½	19	4	26	+++	No (depr.)	1′	8	No	Satisfactory

TABLE IV (*cont'd*)

B. Induction and Maintenance Requiring Change to Other Agents

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication: Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of anaesthesia (min)	Other agent	Duration of maintenance (min)	Relaxation	Apnoea	Analgesia	Eyes open after last dose dolitrone (min)	Phlebitis	
1	E.U.A.; D & C; Biopsy & caut. cervix	146	66½	50	96	400	600	1	15	N_2O-O_2(7:2)-TCE	5	No	No	—	25	No	Violent uncontrollable movements
2	D & C; Biopsy cervix; E.U.A.	122	59	50	85	400	600	1	19	N_2O-O_2(7:2)-TCE	5	No	No	—	41	+	Violent uncontrollable movements
3	D & C; E.U.A.; Cervic. polypectomy	147	70	50	84	380	620	1	24	N_2O-O_2(7:2)-TCE	4	+	No	—	17	No	Moderate uncontrollable movements

thiopental. This property of Dolitrone is more marked following induction. With prolonged administration the respiratory pattern more closely approaches that of sodium thiopental. Tachypnoea under both agents is marked but more pronounced with sodium thiopental following induction than with Dolitrone; again the respiratory rate with both agents is not markedly different after maintenance for 30 minutes at a steady level.

In only three cases was it possible to maintain anaesthesia in an electroencephalographic level comparable for both agents. This was most commonly in upper third level. In all other cases anaesthesia with Dolitrone required markedly deeper levels in order to make the patient tolerate the endotracheal tube. Figure 9 is one example of this. Both tracings are taken in the 18th minute of maintenance. The volunteer had received 375 mg. of sodium thiopental 2.5 per cent for induction and at the time the tracing was taken he had received 860 mg. sodium thiopental 1 per cent. He was in upper third electroencephalographic level. At the second sitting 500 mg. of Dolitrone 2.5 per cent was required for induction and at the time this tracing was taken 2700 mg. of Dolitrone 2 per cent had been administered. Any lighter level of anaesthesia would immediately cause the patient to buck and strain. This tracing shows almost complete absence of brain waves for as long as 18 seconds.

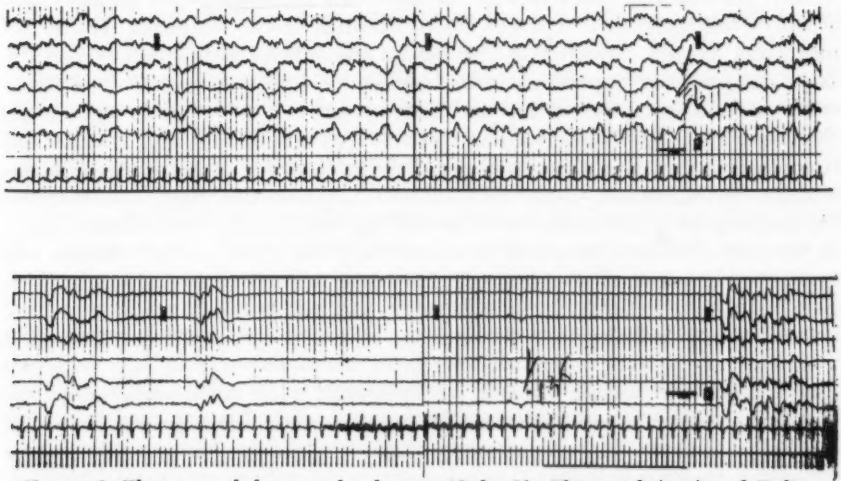


FIGURE 9. Electroencephalogram of volunteer 10 for Na Thiopental (top) and Dolitrone (bottom)—both tracings were taken in the eighteenth minute of maintenance and represent the lightest level at which the endotracheal tube was tolerated.

Even with these markedly deeper levels of Dolitrone anaesthesia spontaneous movements of arms and legs quite frequently occurred throughout the administration. This was also the case in the very deep level of anaesthesia shown on the electroencephalographic tracing which is illustrated here. Only two volunteers did not show these movements at all. Although these occasional movements, which consisted of flexion of arms and legs, did not interfere with our experiments, they can be extremely troublesome under actual operating conditions.

In volunteer 6 these movements were so violent that the experiment could not be concluded. The movements consisted of clonic-tonic flexion of arms and legs, mainly limited to the elbows and knees. These were of such intensity as to make smooth maintenance of anaesthesia impossible despite continuous rapid injection of Dolitrone 2 per cent. Yet the same volunteer had been maintained under the experimental conditions on only 1060 mg. of sodium thiopental. He had required 560 mg. of Dolitrone 2.5 per cent for induction and even after further injections of up to 1540 mg. of 2 per cent Dolitrone for maintenance, the experiment had to be abandoned. This would seem to indicate that Dolitrone is a weak anaesthetic agent with action primarily and almost exclusively upon the cerebral cortex, allowing perhaps preponderance of basic ganglia. This patient also developed severe thrombophlebitis at the site of injection after the experiment, which required physiotherapy because of his inability to fully extend the arm at the elbow. The condition resolved without sequelae in the course of ten days.

When these volunteers were stimulated after they had been satisfactorily maintained at a steady level of anaesthesia, those under sodium thiopental would usually respond with a slight flexion of the legs which subsided immediately the stimulus was removed. As previously mentioned, this stimulus consisted of the insertion of a towel clip at one side of the umbilicus. The movement was usually restricted to the leg on the side of stimulation. When the same stimulus was applied to individuals under Dolitrone, severe clonic-tonic contraction of both legs at hip and knee would invariably result even under the deepest level of anaesthesia, and was slow to subside after the stimulus had been removed. In fact it tended completely to upset for a time the even maintenance of anaesthesia. Both with sodium thiopental and with Dolitrone the electroencephalogram would reveal marked lightening of the level of anaesthesia. In the case of sodium thiopental this would only last as long as the stimulus was applied, whereas with Dolitrone further doses of the drug were needed in rapid succession in order to re-establish the previous level of anaesthesia.

Our findings with regard to the wake-up time after sodium thiopental seemed to confirm the animal findings of Thompson, Smith and Werner (1). With two exceptions all individuals reacted to the spoken word much sooner after the conclusion of the experiment with Dolitrone despite the larger total dose of drug administered. They also seemed to have less of a hang-over and felt better when they were taken home in the evening.

No abnormalities were seen in the electrocardiogram in any experiment with either sodium thiopental or Dolitrone. Neither were there any changes in blood pressure and pulse rates consistent or significant enough to state that there was any marked difference between the two drugs studied. Neither produced marked or prolonged hypotension or significant tachycardia at any time. Post-anaesthetic nausea was not a significant feature with either agent. Except for volunteer 6 who developed severe thrombophlebitis no significant postanaesthetic complications developed.

The *clinical use* of Dolitrone confirms our findings in volunteers. Its outstanding advantage is its respiration-sparing properties which are in sharp contra-

distinction to those of sodium thiopental. Double the sleep dose of sodium thiopental if given rapidly almost invariably produces a period of apnoea frequently associated with transitory hypotension. No such hypotension was seen with Dolitrone. It must be remembered that, if used for induction alone, Dolitrone is much shorter acting than sodium thiopental and the maintenance agent must be immediately started upon induction. Nitrous oxide maintenance after Dolitrone induction is frequently inadequate since the effect of the induction agent is not carried into the early maintenance period for a sufficiently long time.

In the maintenance of anaesthesia Dolitrone is entirely unpredictable and the incidence of unsatisfactory anaesthesia is high. However the most disturbing feature is the high incidence of severe and moderate phlebitis which we have encountered with the 2.5 per cent solution. When substituting a 2 per cent solution for 2.5 per cent solution the agent becomes even less satisfactory as an anaesthetic agent although the incidence of phlebitis is markedly reduced. We have not attempted to give the agent as a 1 per cent continuous intravenous drip primarily because the 1 per cent solution in distilled water is markedly hypotonic and we have been afraid to use such a hypotonic solution in patients. In the light of our clinical experiences it may well have been that some painless induration of the vein at the site of injection developed also in some of our volunteers after Dolitrone. If this happened it was not severe enough to cause the volunteers to return and complain about any discomfort, except volunteer 6 who required active treatment for a very painful arm.

Another most disturbing feature of Dolitrone is the frequent occurrence of spontaneous movements which can assume most violent proportions and cannot be controlled by the rapid injection of even large doses of the drug. They can only be suppressed by a change to other anaesthetic agents.

Analgesia. We have seen very little evidence of residual analgesia under the conditions in which the drug has been used by us. Comparison of group I with the others of the clinical study seems to indicate that residual analgesia in group I cases may have been due more to nitrous oxide than to Dolitrone or perhaps to a synergism of the two. The analgesic and amnesic properties which have been claimed for Dolitrone therefore had to be separately investigated. Since analgesia is a subjective state it was decided that one of us (GMW) should submit to the administration of Dolitrone to decide whether this drug had analgesic properties. No premedication was given. Dolitrone 2 per cent was administered through a Gordh needle in small increments while the subject remained conscious. Within 20 seconds of the injection of 1 ml. of 2 per cent Dolitrone there was some tingling in the fingers which spread increasingly throughout the body and was most marked in hands, lips, and tip of tongue. The eyelids became heavy, it was difficult to focus, and some double vision appeared . The limbs became heavy but muscle power was retained. Both voices and light sensation were markedly increased to the point of unpleasantness. Perspiration appeared soon but was not appreciated by the subject until very much later. Within a few minutes there was a feeling of nausea which was accompanied by circumoral pallor. There was none of the sense of general well-being which is usually associated with the state of general analgesia. On the

contrary the prevailing sensation was a most unpleasant one. Deep touch such as squeezing of the calves was appreciated as such but was most unpleasant. All touching of the skin both by the investigators and by the volunteer himself caused marked tingling. Whenever the subject asked that he be tested by pin prick there was a markedly exaggerated painful impression of a very fine needle being thrust through the skin although, unbeknown to the subject, at times only the hub of the needle was used to make contact with the skin. At other times the investigators inserted a towel clip into the subject's arm and this was not noted at all. It would appear that expected painful stimuli were perceived as such in an exaggerated manner whether they were indeed painful or not, whereas truly painful but unsuspected stimuli were not felt at all. At one time tingling of the forehead was replaced by a vice-like pressure on the forehead. This was caused by one of the investigators pressing mildly in the region of the supra-orbital nerve. Analgesia was definitely more marked in the arm used for injection. The subject felt an irresistible urge to move from time to time because of the great discomfort he was experiencing during the state of analgesia. The experiment lasted for 20 minutes and during that time a total of 260 mg. of 2 per cent Dolitrone was administered. At the conclusion of the experiment the subject felt a great desire to sleep but after one hour he felt fresh enough to get up and continue with his normal activities. The site of the injection was quite painful and the investigators had noticed hardening of the vein in the forearm while the experiment was still in progress. The pain persisted for some four hours and then gradually subsided to a local tenderness. The following morning there was some discolouration but no tenderness although the vein was indurated for some 2½ inches above the site of injection. The subject retained complete recollection of the entire experiment although there was some lack of appreciation of time and the whole experiment seemed somewhat telescoped.

Summary and Conclusions

Dolitrone, a non-barbiturate intravenous anaesthetic agent, has been compared to sodium thiopental in human volunteers. The drug has also been administered to a series of patients undergoing minor surgical procedures. In these clinical cases the drug has been evaluated both as an induction and as a maintenance agent. In a further study the analgesic properties of Dolitrone were assessed.

From these, it would appear that Dolitrone has three principle *desirable properties*:

1. Because of its marked respiration sparing properties, it could be a useful induction agent. It causes practically no apnoea in double the sleep dose and no significant hypotension. No cardiac irregularities were noted.

2. Muscle relaxation for such procedures as pelvic examinations under anaesthesia is often satisfactory but unpredictable.

3. Dolitrone has definite analgesic properties although the state of analgesia is subjectively less pleasant than that induced with nitrous oxide, trichlorethylene, or intravenous procaine. It is reasonable to assume that a more profound state of analgesia may be obtained if suitable premedication is given.

We have been unable to demonstrate any amnesic properties of the drug.

Against these three advantages are set three overwhelming *disadvantages* of the agent:

1. The high incidence of phlebitis, which ranges from mild to very severe, precludes the use of Dolitrone for anaesthesia or analgesia at the present time, except as a single injection for induction of anaesthesia when phlebitis does not seem to be common. However, one must ask: "Is there a need for another intravenous agent when it must be strictly limited to induction alone?" The incidence of phlebitis could probably be reduced if injection were made into the tubing of a running saline infusion. Unfortunately this would entail the administration of undesirably large amounts of normal saline and is therefore not practicable. 5 per cent Dextrose solution which could be given in larger quantities is unfortunately not compatible with the drug.

2. The unpredictability of Dolitrone as a maintenance agent and as far as relaxation is concerned is a serious disadvantage.

3. The frequent occurrence of spontaneous and often uncontrollable movements despite large doses render the agent unsuitable for maintenance of anaesthesia.

The drug was so unsatisfactory in clinical use that it was discontinued in each group after it had been used in a relatively small number of cases.

In conclusion, after weighing the advantages and disadvantages of Dolitrone we do not feel that at the present time it can be recommended as a desirable clinical agent. The analgesic properties of Dolitrone are intriguing; whether or not they can be utilized clinically will depend upon the ability of the chemists to evolve a compound less likely to cause venous irritation.

Acknowledgements

The authors wish to express their gratitude to Dr. S. B. Fowlow who has assisted in the administration of the general anaesthetics and in the recording of the clinical cases. They are also indebted to Mr. R. L. G. Rainbow, Chief Technician, Cardio-pulmonary Laboratory, for technical help with blood and gas analyses and to Mr. R. A. Schneider, Chief Electroencephalographer, for his part in the recording of electroencephalograms.

Résumé

Le dolitrone est un agent anesthésique non-barbiturique pour administration intraveineuse; les auteurs l'ont comparé au thiopental sodium chez des volontaires. Ils l'ont également injecté à un certain nombre de malades devant subir de la chirurgie mineure. Au cours de cette étude clinique, le médicament a été évalué aussi bien comme agent d'induction que comme agent d'entretien. Dans une étude ultérieure, les propriétés analgésiques du dolitrone ont été éprouvées.

De tout cela, il résulterait que le dolitrone possède trois qualités principales désirables:

1. Du fait qu'il n'affecte pas la respiration, il pourrait être un agent bien utile pour l'induction. A une dose double de celle requise pour provoquer le sommeil, il cause peu ou pas d'apnée et pas d'hypotension marquée. Nous n'avons pas dépisté d'irrégularités cardiaques.

2. Le relâchement musculaire pour des interventions comme des examens gynécologiques sous anesthésie est souvent suffisant mais inconstant.

3. Définitivement, le dolitrone a un pouvoir analgésique bien que, subjectivement, cette analgésie soit moins plaisante que celle que procure le protoxyde d'azote, le trilène ou la procaine par voie intraveineuse. Quand on a donné une prémédication adéquate, il y a lieu de croire que l'analgésie est plus poussée.

Il ne nous a pas été possible de démontrer si ce médicament peut produire l'amnésie.

Par opposition à ses trois avantages, ce médicament possède trois désavantages importants:

1. La grande fréquence des phlébites, dont la gravité peut aller de bénigne à massive, proscrit, actuellement, l'emploi du dolitrone en anesthésie ou en analgésie à moins qu'il s'agisse de l'injection d'une seule dose pour faire l'induction d'une anesthésie et cela, seulement, si le malade n'a pas tendance à faire des phlébites. Toutefois, on pourrait se demander: "Y a-t-il lieu d'obtenir un autre agent intraveineux dont l'usage se limiterait strictement à l'induction?" La fréquence des phlébites pourrait probablement être diminuée si l'on faisait l'injection de dolitrone dans la tubulure d'un sérum salé déjà installé dans la veine. Malheureusement, cela entraînerait l'administration de grandes quantités de sérum salé ce qui n'est pas pratique et toujours indiqué. Quant au sérum glucosé 5 pour cent qui pourrait être plus indiqué et administré en plus grande quantité, il est incompatible avec le dolitrone.

2. L'inconstance du Dolitrone aussi bien dans le maintien de l'anesthésie que dans la production du relâchement musculaire devient un désavantage sérieux.

3. L'apparition fréquente de mouvements spontanés et souvent incontrôlables et cela, en dépit de grosses doses, fait que cet agent n'est pas pratique pour le maintien de l'anesthésie.

Ce médicament a donné, en clinique, tellement peu de satisfaction que son emploi a été abandonné à différents endroits après usage dans un nombre de cas relativement restreint.

En conséquence, en pesant bien les avantages et les désavantages du dolitrone, nous ne croyons pas, dans le temps présent, pouvoir recommander cet agent comme bienvenu en clinique. Les propriétés analgésiques du dolitrone posent un problème: elles ne pourront pas être employées en clinique à moins que les chimistes réussissent à en extraire un produit moins irritant pour les veines.

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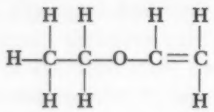
USE OF ETHYL VINYL ETHER FOR GENERAL AND THORACIC SURGERY*

DORIS C. GROSSKREUTZ, M.D.** and DAVID A. DAVIS, M.D.***

ALTHOUGH ethyl vinyl ether was studied and its anaesthetic properties reported in 1930 by Leake and Chen (1), it was not until 1947 that Krantz (2, 3) worked extensively with it in animals and applied it to man. Since 1952 investigations have been made in several clinics throughout the United States and Canada to ascertain a place for this hybrid compound in modern anaesthetic practice.

Chemically ethyl vinyl ether is an asymmetric, unsaturated ether containing an ethyl radical and a vinyl radical, thus offering properties similar to divinyl ether and diethyl ether. It is a clear, colourless liquid with a slightly pungent but



$C_2H_5—O—C_2H_3$

Molecular structure of ethyl vinyl ether

not irritating odour. It has a boiling point of 35.8°C. with a vapor density of 2.49. Although it tends to polymerize and oxidize to aldehydes in the presence of acid, light, and moisture, if treated with 0.01 per cent n-phenyl alpha naphthylamine and 3 per cent absolute alcohol it can be stored for a year tightly stoppered in a cool, dark place. It does not form toxic products with soda lime

TABLE I

PHYSICAL PROPERTIES OF ETHYL VINYL ETHER

Appearance	Colourless, clear
Odour	Slightly pungent
Boiling point	35.8°C.
Specific gravity	0.759 at 20°C.
Molecular weight	72.10
Vapour pressure	485 mm. at 22°C.
Range of flammability	Lower limit in O_2 : 2.1%

in the presence of heat and thus can be used safely in a closed system. Like the other ethers, it forms explosive mixtures; its lower limit of flammability in oxygen

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, Mont Tremblant, P.Q., June 18-20, 1956.

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is at 2.1 per cent concentration so that suitable precautions must be taken to prevent ignition (4).

The margin of safety in dogs has been found by Krantz (2) to be slightly greater than diethyl ether and twice as great as divinyl ether, while the potency of ethyl vinyl ether for induction almost equals that of divinyl ether (3). Dornette and co-workers (5) reported no demonstrable pathological changes in the liver, kidney, lung, and heart after repeated administrations to dogs, while in a similar series using divinyl ether Orth (6) found considerable central necrosis of the liver. Morch (7) saw depression both of respiration and blood pressure in deep planes but this was much less marked than that caused at similar levels with divinyl and diethyl ether.

Clinical Application

Ethyl vinyl ether has been employed in our clinic during the past year on 239 patients for a wide range of surgical procedures. They were unselected, ranging in age from 7 days to 82 years and in weight from 6 to 220 pounds. Although 78 per cent were judged to be in a good physical state, it has been employed in patients with diabetes, bronchiectasis, tuberculosis, thyrotoxicosis,

TABLE II

Ages

Ages	No. of patients	Ages	No. of patients
0–1	13	40–49	35
1–9	64	50–59	28
10–19	31	60–69	8
20–29	33	70–79	2
30–39	25	80 +	1

diminished liver function, cardiac arrhythmias, hypertension, and pyelonephritis. The surgical procedures carried out successfully under ethyl vinyl ether covered all types from simple myringotomies and closed reductions to pulmonary resections and mitral valvulotomies, and lasted from 10 minutes to 7½ hours. This anaesthetic agent has been administered by the open drop, semi-closed with nitrous oxide or ethylene, non-rebreathing, and closed carbon dioxide absorption techniques for both induction and maintenance.

Ethyl vinyl ether permitted a rapid induction in 1½ to 4 minutes by both the open drop and semi-closed techniques. Although the odour annoyed operating room personnel it was readily acceptable to the patient. Being less of an irritant to the respiratory tract than divinyl ether, the incidence of breath-holding and laryngospasm was low. Too rapid administration, however, could cause coughing but this was easily controlled and never paroxysmal with resultant cyanosis as often seen with diethyl ether.

Open drop ethyl vinyl ether proved to be a satisfactory method of analgesia in burn dressings, simple closed reductions, and obstetrical cases, allowing as steady

TABLE III

TYPES OF PROCEDURES

Plastic (including hare lips and cleft palates)			42
Eye–E.N.T. (including laryngectomies)			22
Upper abdominal (including diaphragmatic hernias and gastrectomies)			11
Lower abdominal (including radical hysterectomies)			16
Neurological (including craniotomies and laminectomies)			8
Urological (including nephrectomies)			13
Orthopedic			15
Thyroid and radical neck dissection			7
Oral			4
Minor			12
Obstetrical			4
Intrathoracic			85
Pneumonectomies	10		
Lobectomies	41		
Decortications	4		
Exploratory thoracotomies	13		
Thoraco-abdominal procedures	5		
Cardiac procedures	6		
Patent ductus ligation		2	
Mitral valvulotomies		3	
Pericardectomy		1	

a maintenance of this stage as is obtained with divinyl ether. The intubations performed under ethyl vinyl ether alone were limited to the younger age group under 10 years as the relaxation of the jaw was poor and the cords remained active so that considerable skill was required for an atraumatic intubation. Although unsatisfactory for oral intubation without a muscle relaxant, it proved adequate for blind nasal intubation. Without a previous topical application of a local anaesthetic agent to the larynx and trachea, insertion of the tube caused bucking and bronchiolar spasms which were not, however, as severe as those seen in equally light planes with thiopental or cyclopropane. The major part of these could be subdued within 1 to 3 minutes by deepening of the anaesthetic plane. Excessive salivation previously reported (8) was not noted in this series but all patients had received either scopolamine or atropine before induction. Vomiting on induction did not occur even in the emergency patient owing to minimal irritative properties although this was not true on emergence. Patients with known full stomachs, however, were not given ethyl vinyl ether.

Maintenance of anaesthesia by the various techniques mentioned above was satisfactory in all cases not requiring deep planes of anaesthesia. Depth could be rapidly altered in 30 to 90 seconds as demonstrated by changes in the electroencephalographic tracings. Muscle relaxation, however, was unreliable and although abdominal relaxation was adequate for intraperitoneal procedures in children under 5 years, succinylcholine was required for the opening and closing of the peritoneal cavity in the majority of abdominal cases.

Ethyl vinyl ether was administered to 85 patients undergoing various intrathoracic procedures including cardiac surgery and repair of tracheo-esophageal

TABLE IV

DURATION

Duration	No. of cases	Duration	No. of cases
–½ hr.	15	3–4 hrs.	30
½–1 hr.	44	4–5 hrs.	28
1–2 hrs.	61	5–6 hrs.	17
2–3 hrs.	39	6 + hrs.	5

TABLE V

TECHNIQUE OF ADMINISTRATION

Type	No. of patients
Open drop analgesia	12
Open drop anesthesia	39
Semi-closed with N_2O or C_2H_4	140
Closed CO_2 absorption	32
Non-rebreathing	38
Endotracheal	132

fistulae. After the usual premedication of Nembutal®, Demerol®, and scopolamine, induction and intubation were accomplished under thiopental, succinylcholine, and topical Pontocaine® in all but the infants on whom only inhalation agents were employed. For maintenance ethyl vinyl ether was started immediately after loss of the eyelash reflex, mainly by the semi-closed technique with nitrous oxide or ethylene for the adults and non-rebreathing for infants. Assisted or controlled respiration was used as the situation demanded and a mechanical ventilator was employed in seven of these cases.

Patients were maintained at a level light enough to make it possible for them to move their hands on occasion or wrinkle their brows but no bucking occurred unless carinal stimulation was severe. Electroencephalographic tracing at this stage corresponded to level 2 of diethyl ether anaesthesia.

The most impressive observation was the smoothness and quietness of respiration in the light plane of anaesthesia maintained. As deeper planes were attained there was a gradual decrease in amplitude but rate did not appear to be affected. Adequate inflation of the lung could be accomplished by relatively low positive pressure and an increase in compliance of the lung or a decrease in airway resistance was felt as the respirations were assisted. Laboratory confirmation of this possibility is underway and will constitute a future report. Respiration could be controlled readily within a two-minute period without increasing the anaesthetic concentration and similarly, spontaneous respiration was resumed quickly and smoothly without the bucking on the endotracheal tube which is often seen following the lightening of the plane of anaesthesia when cyclopropane is used to control respiration.

The mechanical ventilator could be introduced readily into the system owing to this ease of controlling respiration and of maintaining such control with minimal amounts of ethyl vinyl ether vapor. Patients would remain on control even though they occasionally moved an extremity. One case was managed on the Jefferson ventilator with semi-closed nitrous oxide and ethyl vinyl ether using 150 cc. over a 6¾ hour period; the patient responded within 5 minutes of discontinuing the anaesthesia.

The rapid shift of the depth of anaesthesia allowed desirable control with the patient coughing at the end of the procedure. No increase in bronchial secretions was noted although bronchiolar spasms developed in 14 per cent of the cases, mainly because of pre-existing secretions or inadequate topical anaesthesia. Sixty per cent of these responded to suction and a slight deepening of the plane; 40 per cent had to be given additional medication of aminophylline or succinylcholine because in these patients deepening was followed by hypotension.

While the effect on respiration was ethyl vinyl ether's greatest asset, the effect on blood pressure was its greatest detriment. The blood pressure remained relatively stable in 76.4 per cent of the cases, increased from 20 to 60 mm. Hg.

TABLE VI

CHANGES IN BLOOD PRESSURE AND PULSE RATE

Blood Pressure			
Increased 20–60 mm. Hg.			11.3%
General Surgical Series		12%	
Thoracic Surgical Series		10%	
Decreased 20–80 mm. Hg.			12.6%
General Surgical Series		6%	
Thoracic Surgical Series		25%	
Due to deepening	14.2%		
Due to turning	16.4%		
Due to rib resection	4.8%		
Pulse			
Increased 20–60 b.p.m.			21%
Decreased 20–40 b.p.m.			9%
Pulse Pressure			
Decreased 20–40 mm. Hg.			12.9%

in 11.3 per cent, and decreased from 20 to 80 mm. Hg. in 12.6 per cent. The increase in pressure seemed to be associated with severe surgical stimulation under light anaesthesia and could be reduced by deepening the plane. In one case carbon dioxide accumulation was definitely incriminated.

Hypotension, for the most part, developed gradually in prolonged surgical cases over a 3- to 5-hour period accompanied by an unchanged pulse rate. In the thoracic series sudden drops of pressure of 20 to 40 mm. Hg. were noted in 16.4 per cent of the cases after the patient was turned into the lateral position, with a spontaneous return to pre-induction levels within 5 minutes in all cases

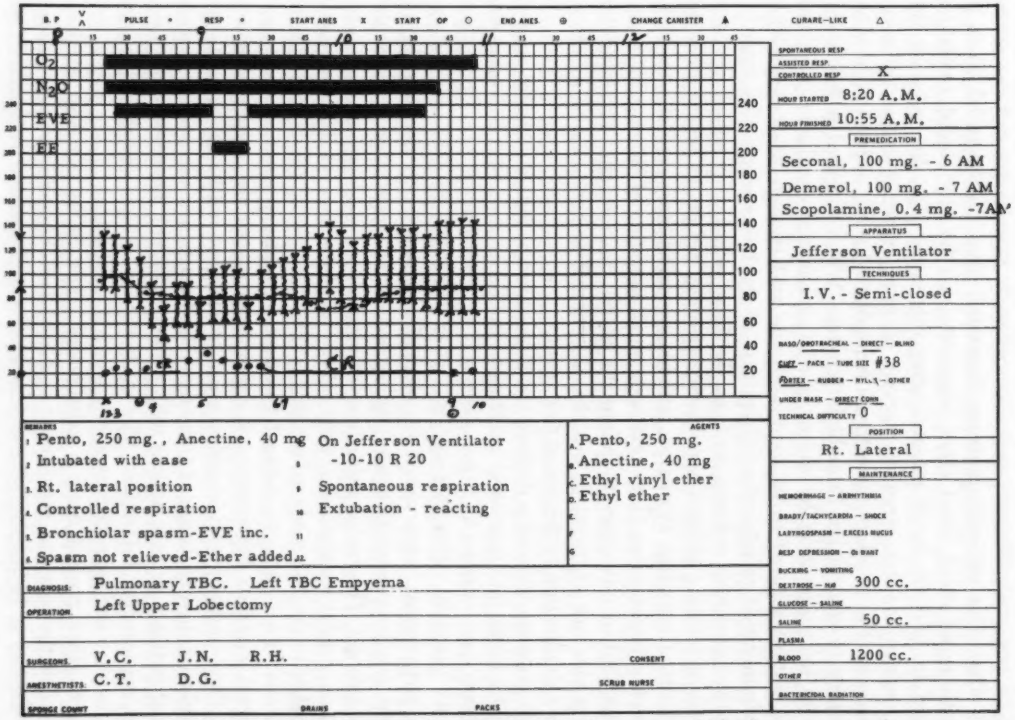

FIGURE 1. This anaesthetic record demonstrates the depression of blood pressure resulting from attempts to deepen the plane of anaesthesia for relief of bronchiolar construction with both ethyl vinyl ether and diethyl ether. The employment of a ventilator with a negative phase seemingly stabilized the cardiac output so that sufficient concentration of ethyl vinyl ether could be added to obtain the depth of anaesthesia needed.

but one. This patient had a hydrothorax and returned to normal only after the pleura was opened. In 4.8 per cent of cases there were severe drops of pressure of 50 to 80 mm. Hg. on stripping the rib and opening the pleura; this was remedied by interruption of surgery and a lightening of the anaesthetic plane.

Hypotension of 30 to 60 mm. Hg. developed on rapid deepening of the anaesthesia in 14.2 per cent; this responded immediately to washing out the excess ethyl vinyl ether. One patient's pressure decreased from 140/80 to 80/40 in 10 minutes with rapid ethyl vinyl ether administration by the closed technique but returned to 140/100 in 10 minutes after this agent was discontinued and high flow oxygen started. Another patient of poor physical status (Fig. 1) could not tolerate the depth of anaesthesia from diethyl ether or from ethyl vinyl ether necessary to control her bronchiolar spasms. When supplied with a negative phase to her respiration by means of the mechanical ventilator, however, her cardiac output seemed to be kept adequate and enough ethyl vinyl ether could be administered to relax the constriction of the lower respiratory tract.

The various autonomic reflexes, such as the hilar reflexes, remained active in the light planes, causing sudden hypotensive periods, but could be obtunded by adequate doses of atropine. Moreover, patients appeared more sensitive to blood loss, developing hypotension from relatively small amounts of haemorrhage and requiring meticulous attention to adequate blood replacement. Pre-induction hypertension was not aggravated, but the presence of hypotension to us represented a contraindication to the use of this agent.

The pulse pressure showed a decrease of 20 to 40 mm. Hg. in 12.9 per cent of the cases. The pulse rate remained unchanged in 70 per cent with a decrease of 20 to 40 beats per minute in 9 per cent and an increase of 20-60 beats per minute in 21 per cent. This increase was seen especially in the younger age group. No arrhythmias were noted by clinical observation to develop during maintenance, while preoperative sinus tachycardia and ventricular extrasystoles were not worsened. The major disturbance found on serial electrocardiographic tracings taken during maintenance with ethyl vinyl ether revealed a descent of the pace maker to the A-V node which was reversed following the termination of the anaesthesia. Two patients showed frequent auricular premature beats and one developed a pulsus bigeminus; all disappeared when the anaesthesia was lightened. Four mitral valvulotomies were performed with no arrhythmias developing during manipulation of the valve. No disturbance was seen by its use in digitalized patients or in a patient with a bundle branch block resulting from a previous myocardial infarction. The arrhythmias which developed under cyclopropane were not seen after changing to ethyl vinyl ether.

Ethyl vinyl ether proved itself a satisfactory agent in 94 per cent of these cases. Clonus of the legs was noted once and mild twitchings in two other cases; response followed a lightening of the anaesthesia and assisted respiration. No generalized convulsions developed, probably owing to the meticulous attention given to adequate oxygenation and prevention of hypercarbia.

Recovery was rapid, with over 50 per cent of the patients awake and moving on the table, the remainder responding within 30-45 minutes. Vomiting did occur about as frequently as following other inhalation agents but was not

prolonged. There were no deaths during surgery and only three in the post-operative period, one from septicaemia, one from coronary thrombosis on the fifth day, and one from pulmonary embolism on the fourth day.

Discussion

As expected from the chemical structure, ethyl vinyl ether possesses properties of both the vinyl and the ethyl radicals. Its volatility, near that of diethyl ether, allows its effective use by the open drop technique yet prevents frosting of the mask and the sudden dangerously high concentration possible with divinyl ether. Its analgesic properties are useful in burn dressings, minor surgical procedures, and obstetrics where anaesthesia is neither desired nor required. Its potency allows a much more rapid induction, quicker emergence, and more facile changes of anaesthetic depth than are accomplished by the use of diethyl ether. It can be administered smoothly by all the modern techniques employed today over a wide range of ages (9) and for relatively long periods of time. Adequate oxygenation with the elimination of carbon dioxide prevents the convulsive tendency inherent in the vinyl radical. This radical when combined with the ethyl radical seems to lose its toxic effect on the liver and kidney as demonstrated by the work of Dornette (5, 10) and Sadove (11).

The poor relaxation developing under ethyl vinyl ether permits orotracheal intubation to be accomplished in only the very young or very weak without the use of a muscle relaxant although it provides adequate conditions for blind nasotracheal intubations. Intra-abdominal procedures cannot be performed with success in a safe plane of anaesthesia as deepening anaesthesia for adequate relaxation will often cause profound hypotension. Adding succinylcholine for the opening and the closing of the peritoneum remedies this problem.

Respirations are well maintained but without the increase in rate often seen in children under diethyl ether. The minimal irritation it causes to the respiratory tract avoids the breath-holding and laryngospasm of too rapid administration of diethyl ether. It can be used in the asthmatic patient, although some severe bronchiolar spasms could not be resolved without causing the hypotension attendant on the deeper planes of anaesthesia with this agent.

This hypotensive effect is the drug's greatest deleterious reaction. If deep planes are avoided, this effect is not troublesome and procedures not requiring relaxation can be managed for many hours with satisfaction and safety. The changes in the electrocardiogram seen during the procedures are benign and mainly limited to a development of nodal rhythm which is no more marked than that developing in similar planes of ether anaesthesia.

The use of ethyl vinyl ether in thoracic surgery has proven to be satisfactory in the majority of cases. The lack of irritative properties to the tracheo-bronchial tree and great potency allow a rapid and smooth change of level of anaesthesia to meet the demands of surgery. The patient can be carried in very light planes without a tendency to react on the endotracheal tube and without exaggerated movements of the diaphragm and mediastinum. The action of the topical agent applied to the larynx must, of course, be considered here in judging this tolerance that develops. Controlled respiration is accomplished with ease without deepen-

ing the patient's level and spontaneous respiration can be re-instituted smoothly without any disturbance of the field of operation. The ease of inflation is quite noticeable and although not all bronchiolar spasms can be controlled at a level of anaesthesia not initiating hypotension, the relaxation of the bronchiolar muscles is as satisfactory as with diethyl ether. The greatest disadvantage found in this thoracic series is, again, the instability of blood pressure as hypotension can develop on turning the patient as well as on stripping the rib. It is indeed difficult to evaluate the hypotension which develops in these cases: here a situation exists where there is concomitant blood loss and severe surgical trauma in patients of poor physical state usually having an inadequate total blood volume. But it seems probable that this agent has a depressant effect on the peripheral vascular system with some direct cardiac action resulting in decreased heart force. Although the pressure returns to control levels in 5 to 10 minutes without medication, the drop in pressure is highly undesirable especially in patients with coronary insufficiency. Mechanisms compensating for blood loss are depressed and blood replacement must be meticulous. The relative stability of the conductive system of the heart under ethyl vinyl ether and the ease of maintaining light planes make the drug attractive for cardiac surgery. The rapid emergence with early return of protective reflexes and consciousness is valuable in these thoracic procedures. The flammability, however, deters one from the use of the cautery that often is desirable. Postoperative morbidity and mortality compare very favourably with those for diethyl ether.

Although this drug is not the answer to our search for the ideal anaesthetic agent, it has qualities which make it useful if its limitations are respected. Employing it for procedures that require only analgesia or first plane anaesthesia and avoiding those requiring relaxation, one has available an agent that has desirable controllability and rapidity. Addition of muscle relaxants makes unnecessary the high concentrations of this agent which can result in an unstable peripheral circulatory system. With strict adherence to the principles of good anaesthetic management this drug proves valuable particularly in the management of intrathoracic procedures.

Summary

1. Ethyl vinyl ether is a useful anaesthetic drug in all ages and for all operative procedures not requiring muscle relaxation or the use of the cautery.

2. It is an adequate and safe analgesic agent by the open drop technique or as an adjunct to nitrous oxide and ethylene.

3. It can be employed in the non-rebreathing, semi-closed, or closed carbon dioxide absorption techniques.

4. Its advantages are rapid induction, emergence, and shift of level of anaesthesia.

5. Its disadvantages are hypotension in the deeper planes of anaesthesia and lack of reliability of muscle relaxation.

6. It has proven to be a satisfactory agent for thoracic procedures if one is very careful to prevent the hypotension which may develop.

Acknowledgment

The authors wish to express their appreciation to Dr. A. H. Neeley and the Ohio Chemical Company for furnishing the ethyl vinyl ether "Vinamar" used in this study.

Résumé

L'éther éthyl vinylique est un éther asymétrique non saturé contenant un radical éthyl et un radical vinyl; il possède ainsi des propriétés semblables à l'éther divinylique et à l'éther diéthylique. C'est un liquide clair, incolore, possédant une odeur légèrement piquante mais non irritante. Son point d'ébullition est à 35.8°C et ses vapeurs ont une densité de 2.49. Bien qu'il aie une tendance à se polymeriser et à s'oxider en aldehydes en présence d'acide, de lumière ou de champignons, on peut l'emmagasiner pendant un an lorsque, fermé hermétiquement et conservé dans un endroit frais et à l'abri de la lumière, il a été traité, au préalable, avec 0.01 pour cent n-phenyl alpha naphthylamine et de l'alcool absolu à 3 pour cent. Avec la chaux sodée, il ne forme pas de produits toxiques mais il est inflammable: la limite inférieure de l'inflammabilité dans l'oxygène étant de 2.1 pour cent.

L'éther éthyl vinylique est un médicament utile à tous les âges et pour toutes sortes d'opérations ne réquérant pas de relâchement musculaire ou de cautère. C'est un agent analgésique de toute sécurité soit en goutte à goutte, soit en complément du protoxide d'azote ou de l'éthylène. On peut l'employer en circuit semi-ouvert, semi-fermé ou fermé avec absorption du CO_2. Ses principaux avantages sont: une induction rapide, un changement rapide de plan d'anesthésie. Ses désavantages sont: dans les plans profonds d'anesthésie, de l'hypotension, ensuite une inconstance dans le relâchement musculaire. En chirurgie thoracique, il s'est avéré un agent satisfaisant, mais il faut être attentif pour prévenir l'hypotension qui peut s'installer.

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THE CLINICAL USAGE OF NERAVAL*

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DR. HAROLD GRIFFITH, in his address before this meeting one year ago, made the prediction that, within the next ten years, hundreds of new drugs would be produced and tested clinically as anaesthetic agents (1). Today, a short twelve months later, that prophecy already is becoming fact, and a number of these agents have appeared upon the anaesthesiologist's horizon. Among these, there are at least two new ultra-short-acting intravenous barbiturates that, on the basis of available data from laboratory experimentation, warrant further clinical trial and study.

There is a certain justification for the continuing search aimed towards the introduction of a more desirable intravenous anaesthetic agent. The drugs of this type which are presently available have been eminently successful in revolutionizing anaesthetic practices within the past two decades: they have effectively abolished the fear of anaesthesia, and they have made the prolonged, stormy inductions of an earlier day a thing of the past. They have not, however, proved to be ideal drugs on a number of counts. These barbiturates often have acted as selective depressants of the medullary centres, particularly the centres controlling respiratory activity and vasomotor tone. Respiratory depression and hypotension occasionally have been alarming in degree following administration of these drugs. Furthermore, parasympathomimetic effects have been exhibited which have resulted in such induction complications as coughing, sneezing, laryngospasm, and hiccups; these phenomena, while usually merely annoying, have on other occasions been truly dangerous. Finally, and of most importance, the ultra-short-acting barbiturates have been shown to be, in fact, rather slowly metabolized (2) (3) (4) (5) (6). Convincing evidence has been amassed to demonstrate that the apparently short duration of thiobarbiturate anaesthesia is dependent upon a relatively rapid redistribution of plasma levels of the drug into the fat depots, from which it is slowly liberated and metabolized. Minimal doses thus are of short duration, but larger doses produce prolonged hypnosis. This drawback has intensified the search for a thiobarbiturate that is metabolized more rapidly in the body and will thus permit better control of the anaesthetic state: Neraval Sodium has been suggested as just such a drug.

CHEMISTRY AND PHARMACOLOGY

Neraval Sodium[1] is the sodium salt of methyl-thio-ethyl-2'-pentyl-thiobarbituric acid.

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society, Mont Tremblant, P.Q., June 18-20, 1956.

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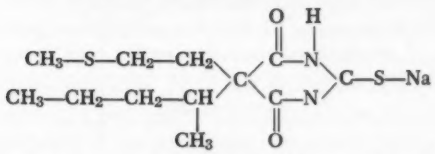
[1]Generous supplies of Neraval Sodium were made available to the authors during these studies by the Schering Corporation, Bloomfield, New Jersey.



The compound is unique among the thiobarbiturates in that it contains two sulphur atoms, there being a methyl-thio-ethyl radical at the 5 carbon atom in addition to the sulphur atom at the 2 carbon position as is found in the more familiar Pentothal and Surital. The relationship of this methyl-thio-ethyl radical to the essential amino acid, methionine, has been commented upon (7), and it has been postulated that the presence of this radical may be of importance in the detoxification process of the drug.

In animals, the intravenous administration of Neraval solution promptly induces an anaesthetic state that is characterized by its brevity and by the rapid recovery period. The intravenous administration of either 40 mgm./kgm. of Neraval or 25 mgm./kgm. of Pentothal produced a similar depth and duration of surgical anaesthesia in the dog; the same was true of 30 mgm./kgm. doses of Neraval and 18 mgm./kgm. doses of Pentothal in the monkey. The anaesthetic potency of Neraval is thus approximately two-thirds that of Pentothal in both species. At these dosage levels, which produced comparable depths and duration of anaesthesia, complete recovery, as estimated by a return to a co-ordinated walk, was significantly more rapid following the administration of Neraval than after anaesthesia produced by Pentothal (8).

Clinical Studies

The clinical usage of Neraval has been studied extensively in Europe, particularly in Germany (9), for the past two years, but interest in the drug is of far more recent origin on this continent (7) (10). The present investigations were based upon 300 clinical administrations of Neraval, and were designed primarily to elucidate the effects upon the functions of the vital medullary centres, to enumerate the incidence of parasympathomimetic complications during the induction period, and to evaluate the recovery time following anaesthesia. All results have been expressed as arithmetic means, and, where practicable, have been subjected to appropriate statistical analysis.

The first phase of investigation consisted of one hundred operations of relatively short duration, dilatation of the cervix and curettage of the uterus, performed on one hundred patients, fifty of whom were anaesthetized with a 2½ per cent solution of Pentothal (the standard ultra-short-acting thiobarbiturate presently in use in the Department of Anesthesiology at the Hartford Hospital), and fifty with 2½ per cent solution of Neraval (Table I). Every effort was employed to produce two comparable series. Only risk one patients, with normal hematocrits, were selected for either series. The ages and weights of the patients in each series were not statistically different: the average age of the patients receiving Pentothal was 40.2 ± 1.60 years, while that of the patients receiving Neraval was 37.5 ± 1.95 years; the average weight of the patients receiving Pentothal was

TABLE I

COMPARISON OF NERAVAL AND PENTOTHAL IN COMPARABLE SERIES OF D. AND C.'s

	Pentothal 2½%		Neraval 2½%		
Patients	50		50		
Age (years)	40.2	1.60	37.5	1.94	$p>0.05$
Weight (pounds)	138.0	3.65	133.9	3.35	$p>0.05$
Induction time (seconds)	75.1	3.46	160.8	9.65	$p<0.01$
Induction dose (mgm.)	252.9	13.34	431.5	23.75	$p<0.01$
Induction dose (mgm./lb.)	1.86	0.079	3.25	0.152	$p<0.01$

138.0 ± 3.65 pounds, while the average weight of the patients receiving Neraval was 133.9 ± 3.35 pounds. The drugs and doses employed for premedication were approximately the same in each series, and generally consisted of an oral barbiturate (Seconal or Nembutal) two hours prior to the induction of anaesthesia, and the hypodermic administration of an opiate (morphine sulphate or Demerol) one hour before operation. All the patients were anaesthetized by a single anaesthesiologist, and the same technique was employed in each instance.

The barbiturate drug was injected into the tubing of a free-flowing intravenous infusion at a standard rate of 6 cc. of Pentothal per minute or 12 cc. of Neraval per minute. The induction time was measured in seconds from the beginning of barbiturate injection to the loss of the eyelash reflex, and averaged 75.1 ± 3.46 seconds for Pentothal and 160.8 ± 9.65 seconds for Neraval, a difference that is highly significant from the statistical viewpoint. The difference between the amount of each drug that was required to effect induction also was highly significant on a statistical basis: the average induction dose of Pentothal was 252.9 ± 13.34 mgm., as compared to an average induction dose of 431.5 ± 23.75 mgm. of Neraval. The induction dosage was calculated on a weight basis, and found to average 1.86 ± 0.08 mgm./lb. for Pentothal, and 3.25 ± 0.15 mgm./lb. for Neraval.

The effects of the two drugs upon certain vital functions were evaluated in each series of patients immediately following induction, and are recorded as the

TABLE II

COMPARISON OF NERVAL AND PENTOTHAL IN COMPARABLE SERIES OF D. AND C.'S: EFFECTS

	Pentothal	Neraval
Blood pressure	− 10.32%	− 12.20%
Pulse rate	− 11.16%	− 12.06%
Respiratory Rate	− 11.14%	− 6.58%

arithmetic mean of the percentage of change from the resting preoperative values (Table II). The systolic blood pressure decreased an average 10.32 per cent following the induction of anaesthesia with Pentothal, and 12.20 per cent

following induction with Neraval. Pulse rate also was decreased by both drugs, the decrease amounting to 11.16 per cent of the pre-operative value following induction with Pentothal and 12.06 per cent following induction with Neraval. The respiratory rate was decreased 11.14 per cent when Pentothal was employed for induction, but only 6.58 per cent when Neraval was the anaesthetic agent. The increased susceptibility of the respiratory apparatus to the effect of Pentothal in comparison to that produced by Neraval also is suggested by the fact that induction doses of Pentothal resulted in apnoea in 3 of the 50 patients, while apnoea occurred in only one of the fifty patients receiving Neraval.

Induction was considered complete following the loss of the eyelash reflex, and nitrous oxide–oxygen, at flow rates of 5.5 and 2.5 litres per minute, were then administered by the semi-closed, circle filter carbon dioxide absorption technique. The need for subsequent intravenous increments of barbiturate was determined by the urgency, depth, and rate of respiration; the tone of the muscles of the fingers; and the occurrence of limb movement: in all instances an attempt was made to maintain as light a plane of anaesthesia as was compatible with the exigencies of the operative procedure (Table III). The total duration

TABLE III

COMPARISON OF NERAVAL AND PENTOTHAL IN COMPARABLE SERIES OF D. AND C.'S: DURATION

	Pentothal 2½%	Neraval 2½%	
Anaesthesia time (minutes)	15.7 ± 7.09	19.6 ± 1.27	$p>0.05$
Total dose (mgm.)	429.6 ± 20.0	693.5 ± 25.26	$p<0.01$
Total dose (mgm./lb.)	3.12 ± 0.12	5.26 ± 0.19	$p<0.01$
Reflex time (from last dose)	12.70 ± 0.93	14.18 ± 0.94	$p>0.05$
Waking time (from last dose)	28.35 ± 6.94	29.57 ± 2.89	$p>0.05$

of anaesthesia was not statistically different between the two series, amounting to 15.7 ± 7.09 minutes in the patients receiving Pentothal and 19.6 ± 1.27 minutes in those patients receiving Neraval. There was a significant difference in the total dose of each drug required, however, the total dose of Pentothal averaging 429.6 ± 20.0 mgm., and that of Neraval averaging 693.5 ± 25.26 mgm. Calculated on a milligram-per-pound basis, the total dose of Pentothal was 3.12 ± 0.12 mgm./lb., while the total dose of Neraval was 5.26 ± 0.19 mgm./lb.

Reflex time was measured in minutes from the time of administration of the last dose of barbiturate to the time required for the return of reflex activity, such as swallowing, masseter tone, or the eyelash reflex. It averaged 12.70 ± 0.93 minutes following the use of Pentothal, and 14.18 ± 0.94 minutes after anaesthesia produced by Neraval, a difference that is not statistically significant. Waking time was measured from the time of administration of the last dose of barbiturate to the moment at which the patient opened her eyes and responded verbally to questions. The waking time following Pentothal anaesthesia averaged 28.35 ± 6.94 minutes, as compared to 29.57 ± 2.89 minutes following Neraval anaesthesia: the difference between these two waking times is not of statistical significance.

A noticeable difference in the frequency of such complications as hiccup, coughing, sneezing, and laryngospasm was noted during the induction of anaesthesia in these two series of patients: they occurred in 8 of the 50 patients anaesthetized by Neraval, but in only one of the 50 patients anaesthetized by Pentothal. It was considered possible that the occurrence of these complications might be related to the speed of administration of Neraval, or to the concentration of the drug that was achieved initially in the blood stream and/or tissues (Table IV). The effects of four different concentrations of Neraval upon the incidence of these induction complications were therefore investigated in four groups of patients. Fifty patients were induced slowly with an intravenous infusion of 0.4 per cent Neraval in 5 per cent glucose and water, and only one instance of hiccup was encountered in this series of patients. A total of 180 inductions were

TABLE IV

COMPLICATIONS DURING NERAVAL INDUCTIONS

	0.4%	2.5%	5%	10%
Patients	50	180	50	20
Burning, pain on injection	0	0	3	2
Hiccups	1	11	3	2
Coughing, sneezing	0	3	2	2

effected with 2.5 per cent concentration of Neraval; hiccups occurred in 11 patients, and coughing or sneezing in 3 others. A third group of patients, numbering 50, were induced with 5 per cent concentration of Neraval: hiccups were produced in three patients, and coughing or sneezing in two others. Three of the patients in this series complained of burning or pain during the administration of Neraval, despite the fact that injections were made into the tubing of a free-flowing intravenous infusion of 5 per cent glucose and water. A final 20 patients were induced with 10 per cent concentration of Neraval: 2 patients complained of burning or pain during injection, 2 more developed coughing or sneezing during induction, and 2 began hiccupping. The hiccups in the latter two patients were extremely severe, in one instance lasting one and a half hours, and forced the curtailment of any further investigation of the use of a 10 per cent concentration of Neraval.

A final group of twenty-six patients was investigated for the purpose of determining the exact duration of action of Neraval in comparison with Pentothal. These patients were undergoing electroshock therapy, and each patient received EST on numerous occasions, frequently on an "every day" or "every other day" basis. An opportunity was therefore afforded for the alternate administration of Neraval and Pentothal to the same patient at the time of successive treatments, each patient serving as his or her own control. All of the patients included in this series received each drug on two or more occasions, and there was a total of 68 administrations of Neraval and 67 administrations of Pentothal to the 26 patients constituting this phase of the study. Thus, the effects of the two drugs could be compared on the same patient, and in addition the multiple adminis-

trations of each drug to the same patient served to minimize the experimental errors of observation.

No premedication was employed prior to the induction of anaesthesia. Venipuncture was performed, preferably in a vein of the antecubital fossa, with the patient lying supine in bed. The patient was then asked to hold the contralateral arm above the bed, and the injection of 2½ per cent Pentothal at a rate of 1 cc. every five seconds, or 2½ per cent Neraval at a rate of 2 cc. every five seconds, was carried out. All times were measured in seconds, by stopwatch, from the time of the beginning of the injection of the barbiturate (Table V). The induc-

TABLE V

COMPARISON OF NERAVAL AND PENTOTHAL DURING ELECTROSHOCK THERAPY
(All times measured in seconds)

	Pentothal	Neraval	
Induction time	53.8 ± 3.59	118.1 ± 11.02	$p<0.01$
Sleeping time (end of induction to response)	466.3 ± 18.87	399.1 ± 17.40	$p<0.01$
Total anaesthesia time (start of induction to response)	520.3 ± 19.72	517.3 ± 16.12	$p>0.05$

tion time of Pentothal was determined from this zero point to the moment when the arm held in the air dropped to the bed, and averaged 53.8 ± 3.59 seconds. The induction time of Neraval, which was administered at a rate that was twice as fast as that employed for Pentothal, was determined in similar fashion, except that the injection of Neraval was discontinued when a dose had been administered that was twice as large as that required to effect induction in the same patient with Pentothal. This variation in technique was based on the earlier observations of the differences in potencies and induction times between Pentothal and Neraval which were made during the first phase of these investigations, and was introduced to prevent a discrepancy between the comparative doses of the two drugs. The induction time following the administration of Neraval averaged 118.1 ± 11.02 seconds, and thus differed to a highly significant degree from the induction time following the administration of Pentothal.

At the end of induction, a standard dose of Anectine, varying from 40 to 60 mgm. in accordance with the weight and body build of each individual patient, was administered; and the patient was inflated with oxygen by rhythmic manual compression of a breathing bag attached to a face mask until all muscular fasciculations had ceased. Electroshock was then applied, and artificial ventilation was resumed following the convulsion and maintained for the duration of the apnoeic period. A determined effort was made to avoid either hyper- or hypoventilation. The patient's forearm and hand were then pricked every 15 seconds with a pin until the end-point response occurred, shown by the withdrawal of the hand or arm. Spontaneous respirations always occurred prior to this reaction to stimulation, eliminating the possibility that the time of reaction might coincide with, and indeed be dependent upon, recovery from the effects of the relaxant drug.

This experimental method permitted the determination of the total anaesthesia time, measured from the start of induction to the moment at which reaction to stimulation occurred, as well as the determination of the sleeping time, measured from the end of induction to the time of reaction to stimulation. The sleeping time following the administration of Neraval averaged 399.1 ± 17.40 seconds and was significantly shorter in comparison to the average of 466.3 ± 18.87 seconds when Pentothal was the anaesthetic agent. The total anaesthesia time, however, was no different following the use of the two drugs, averaging 520.3 ± 19.72 seconds for Pentothal and 517.3 ± 16.12 seconds for Neraval.

Discussion

The results of these studies have served to confirm some of the clinical impressions formed by previous workers regarding the usages of Neraval sodium (7) (10), but have been at variance with other aspects of those opinions on certain points. The induction dose and the total dose of Neraval, both on an absolute and on a milligram-per-pound basis, are greater than for Pentothal, the ratio being 1.7:1. The induction time is more than twice that of Pentothal, even when allowance is made for the greater potency of the latter drug by the more rapid administration of a larger dose of Neraval. As one patient phrased it, "It's taking a lot longer to go to sleep than the last time I had Pentothal." In most instances, the longer induction time has been of no clinical importance; but on certain occasions, particularly in agitated patients being anaesthetized for electroshock therapy, the prolonged induction has been a definite disadvantage.

The effect of Neraval upon the medullary centres has followed, in general, the pattern seen when other ultra-short-acting thiobarbiturates are employed for the induction of anaesthesia. The systolic blood pressure has been depressed to a minor extent, amounting to a 10 per cent decrease from the preoperative level, but in no instance did the hypotension become alarming in degree. The pulse rate was often unchanged, but in a number of patients there was a definite tendency towards a mild and transient bradycardia. The respiratory rate was depressed in the majority of the patients receiving Neraval, but to a less extent than when Pentothal was employed for induction.

The parasympathomimetic activity of Neraval has produced a number of induction complications with a much greater frequency than is usually encountered following induction with the other commonly employed thiobarbiturates. The occurrence of hiccups, laryngospasm, and coughing or sneezing is not alarming to the experienced anaesthesiologist (7); but the fact remains that these are not desirable phenomena during the induction of anaesthesia, and their high incidence following the administration of Neraval must be considered a definite disadvantage of the drug. This is particularly true when they persist well into the postoperative period, as occurred with one patient who developed hiccups following the use of a 10 per cent solution of Neraval, as cited above. The occurrence of parasympathomimetic activity seemed to increase proportionately with increase in the concentration of Neraval employed. Concentrations of Neraval greater than 2.5 per cent also were irritating on occasion, causing the

patients to complain of burning and pain at the site of injection and along the course of the vein during the administration of the drug.

The sleeping time following the use of Neraval in a carefully controlled series of patients undergoing electroshock therapy was definitely shorter than that observed in the same patients on other occasions when anaesthesia was produced by Pentothal. The total anaesthesia time was the same for both drugs, however, the shorter time following Neraval being offset by the longer induction time required with that drug. Observations of reflex and waking time in the less well controlled series of patients undergoing dilatation and curettage showed no significant difference as between the two drugs. The use of a continuous infusion of 0.4 per cent Neraval for operations of long duration (one to three hours) suggests the possibility that the hypothecated rapid metabolism of Neraval may be more demonstrable following procedures of greater duration than those studied in these investigations. However, it is the consensus of many investigators that all thiobarbiturates owe their apparent rapid action to a redistribution of the drug from the plasma to fat, and that the search for better intravenous anaesthetic agents should be directed towards compounds other than the thiobarbiturates (11).

Summary

1. The use of Neraval has been studied during the course of 300 clinical administrations.

2. The induction time of Neraval is more than twice that of Pentothal.

3. Both the induction dose and the total dose of Neraval are 1.7 times that of Pentothal.

4. The effect of Neraval upon the vital medullary centres is similar to that of other ultra-short-acting thiobarbiturates, although there is suggestive evidence that the drug may be less depressing to the respiratory centre.

5. Parasympathetic activity is occasionally quite marked during induction with Neraval, and is manifested by the occurrence of hiccups, coughing, and sneezing or laryngospasm.

6. Concentrations of Neraval above 2.5 per cent may be irritating to the veins into which the drug is injected.

7. Waking time following a sleeping dose of Neraval is shorter than that following Pentothal.

Résumé

Le neraval sodium est un sel de sodium de l'acide methyl-thio-éthyl-2'-pentyl-thiobarbiturique. Parmi les thiobarbituriques, ce composé est le seul à posséder deux atomes de sulfure; il possède un radical methylthio-ethyl aux cinq atomes de carbone en plus d'une atome de sulfure aux deux positions de carbone comme on les trouve dans les deux produits plus connus: Pentothal et Surital. On a fait des commentaires (7) sur le rapport entre ces radicaux et le principal amino-acide, methionine, et il a été émis comme opinion que ce radical pourrait bien avoir une certaine importance dans la détoxification du produit.

Les auteurs ont fait une étude clinique du Neraval sur 300 malades.

Comparée à celle du pentothal, la vitesse d'induction du neraval est deux fois plus lente. Comparée au pentothal, la dose requise pour l'induction aussi bien que la dose totale équivaut a 1.7. Sur les centres médullaires vitaux, le neraval produit des effets semblables à ceux des thiobarbituriques à action très courte, bien que les auteurs soient portés à croire que ses effets sur le centre respiratoire soient moints dépresseurs. Au cours de l'induction avec le neraval, on peut observer occasionnellement une prédominance parasympathique assez marquée: elle se manifeste par le hoquet, la toux, l'éternuement ou le spasme laryngé. A des concentrations supérieures à 2.5 pour cent, le neraval devient irritant pour les veines où on l'injecte. A la suite de l'administration d'une dose anesthésique de neraval, le réveil est plus précoce qu'avec le pentothal.

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CLINICAL INVESTIGATION OF VIADRIL*

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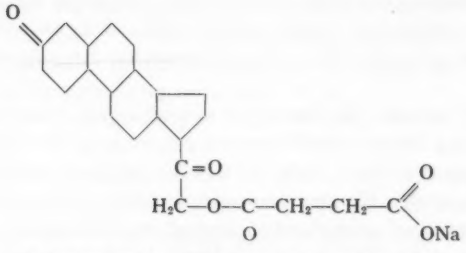
THE anaesthetic activity of steroid hormones in animals was reported by Selye in 1941 (1, 2). In 1942 the same author reported on the anaesthetic activity of 75 steroid compounds, and drew attention to the fact that Pregnanedione possessed anaesthetic activity but no hormonal activity (3, 4). In 1955 Laubach, P'an, and Rudel (5) suggested from animal studies that 21-hydroxypregnanedione sodium hemisuccinate (hydroxydione) might prove to be a satisfactory anaesthetic agent. The formula of this substance is shown below. This compound was prepared by the Pfizer Company under the trade name "Viadril,"[1] and clinical trials in 125 patients were reported by Murphy, Guadagni, and Debone in 1955 (6).



21-hydroxypregnanedione sodium hemisuccinate

The drug is supplied as a white powder which is readily soluble in water. Since it is a soap, it tends to foam, and this characteristic can be a nuisance in the preparation of solutions. It is irritating to tissues and tends to produce thromosis of veins.

METHODS

During the early phases of this investigation, and until we had familiarized ourselves with the characteristics of the drug, we confined its use to female patients undergoing uterine curettage. This selection had the advantages of short duration of anaesthesia, a standard surgical procedure which of itself caused no postoperative discomfort likely to produce restlessness or to require sedation, and a group of patients who were generally in good health. Following experience in these patients, we were able to develop a basis for adjustment of techniques

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, Mont Tremblant, P.Q., June 18-20, 1956.

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[1]We wish to thank Pfizer Canada for making available to us the Viadril used in this study.

and dosage before proceeding to use the drug in operations requiring deeper and more prolonged anaesthesia.

1. *Dosage and Techniques*

All patients in this series received a preoperative medication consisting of Demerol 100 mgm. or morphia gr.1/6 combined with Atropine gr.1/150 or gr.1/100. We commenced our investigation by giving a standard dose of 500 mgm. Viadril to each patient for the operation of dilatation and curettage. When the eyelid reflex had been lost, nitrous oxide and oxygen were administered in a high-flow semi-open system in a ratio of 75 to 25 per cent. Shortly it became evident that the dosage scale must be adjusted on a weight basis, and analysis of our experience suggested an initial dosage of Viadril of 5 mgm. per pound body weight. This proved adequate for curettage when associated with nitrous oxide, but was inadequate for more painful operations. An increase of the initial dosage to 7.5 mgm. per pound body weight was found adequate in all circumstances in which we employed the drug in this study.

Early in our experience we tried dilute solutions of 0.1 and 0.2 per cent of the drug in an intravenous drip infusion. This technique was abandoned because it prolonged the induction period unduly, did not improve controllability, and at the same time presented the necessity of giving large amounts of intravenous fluids.

The control of anaesthesia during more prolonged operations was a problem, because of the long latent period between injection of the drug and its maximum effect. It was apparent very early in this investigation that administration "on demand" was impracticable, because administration of additional Viadril when signs of a lightening of anaesthesia occurred was too late to stabilize the situation. Experience suggested that an additional dose should be given twenty minutes after the first, and further dosage each half hour. The doses which proved satisfactory in most of the patients in this study were 50 per cent of the original dose twenty minutes after induction, and 25 per cent of the original dose subsequently. If signs of lightening anaesthesia occurred it was necessary to use another drug to stabilize the situation, and we used Demerol 50 mgm. intravenously for this purpose. In four cases Viadril was given as a continuous infusion during operation in solution in normal saline. In two cases this solution was 0.1 per cent in concentration and in the other two 0.2 per cent. In all other cases the drug was injected in a 2 per cent solution into the rubber tubing of a rapidly running intravenous infusion of normal saline or 5 per cent Glucose in distilled water. The rate of injection was such that the total initial dose was given within five minutes of commencement.

Observations

We have used Viadril as an anaesthetic agent in this study in 100 patients undergoing a variety of surgical procedures. The nature of the operative procedure in these cases is indicated in Table I. The total dosage of Viadril varied from 500 mgm. to 3500 mgm.

TABLE I

OPERATIONS PERFORMED WITH VIADRIL

Dilatation and curettage	41
Laparotomies	9
Vaginal repair	4
Prostatectomy	2
Head and neck (major)	4
Bronchoscopy and oesophagoscopy	6
Operations on extremities	17
Other miscellaneous operations	11
Supplement for regional anaesthesia (includes 1 Caesarean)	6

In these patients we have studied the length of time from injection of the drug until the loss of the eyelid reflex occurred, the time required for response to calling of the name and for return of full consciousness after operation, the influence of Viadril on the cardiovascular function, respiration, and electroencephalogram records. We have also noted the occurrence in the postoperative period of venous thrombosis, nausea and vomiting, headache, and pulmonary complications. The urine of 20 patients was investigated for the presence of albumin and blood in the postoperative period.

1. *Induction*

The induction period is prolonged with Viadril. All patients were asleep within five minutes of the beginning of the injection, where the injection was completed within five minutes. Eyelid reflex disappeared in every case before ten minutes had elapsed, and in some cases as early as six minutes from the beginning of the injection. In four cases in which a continuous infusion of dilute solution of the drug was used, induction time was prolonged, the patient did not go to sleep for eight minutes to ten minutes, and the lid reflex was lost at about fifteen minutes from the beginning of the infusion.

In all cases the induction was extremely smooth. No patient complained of any vertigo, dizziness, or other unpleasant sensation. Three patients remarked that the room was turning green just before they went to sleep, and one had the same experience with red colour just before going to sleep. In no case did we encounter any excitement during the induction. This induction, on the whole, appeared more to resemble the normal sleep process than that with any other drug to which we can compare it.

The rate of injection of the 2 per cent solution of Viadril during induction appeared to be of some importance in relation to the production of venous thrombosis. It was noted on several occasions when the injection was made at such a rate as to stop or almost stop the intravenous drip, that the patient complained of pain in the arm. Where the rate of injection was timed so that the rate of the drip of the infusion was not perceptibly or very little, slowed, there was no such complaint of pain.

2. *Recovery*

Nitrous oxide was used as an adjunct to Viadril in all cases. Patients who were given a dose of Viadril calculated on the weight basis previously described responded to name in about twenty minutes from the loss of the eyelid reflex, in each case. At this point the patient if left undisturbed would return to sleep. Full consciousness with complete orientation was usual at the end of thirty minutes. In other operations where the drug was used in conjunction with nitrous oxide, waking time in response to the patient's name after stopping nitrous oxide administration appeared to vary almost directly with the length of operation and the amount of the Viadril administered in the doses subsequent to the induction dose. In patients receiving a single dose for operations such as uterine curettage, response occurred from immediately at the end of operation to ten minutes after the conclusion of the operation; the patients were wide awake and fully orientated in periods varying from ten minutes to forty-five minutes. The only factor which appeared significant in this variation in awakening time was age, but we could not determine statistically that there was a definite correlation. It would appear that patients show wide variations in respect to awakening time following administration of Viadril, as they do following the use of other anaesthetic agents.

Patients who had larger doses of Viadril (exceeding 1000 mgm.) required a longer period of time to respond after the conclusion of operation. Times for the initial response to the name in this group varied from five minutes to sixty minutes, the majority requiring from fifteen to twenty minutes for the first response. Awakening to full consciousness and orientation in this group was delayed from twenty-five to one hundred minutes, the majority requiring forty to forty-five minutes for complete recovery of orientation after the conclusion of operation. Here again a wide individual variation from patient to patient is evident.

3. *Cardiovascular System*

Pulse rate varied considerably during Viadril anaesthesia, the usual change from the state before induction being a slight increase, which was exaggerated by surgical stimulation in light anaesthesia. In no case was a large variation in pulse rate seen. No arrythmia occurred. Hypotension was rarely seen in the series. We have cast hypotension as a drop in systolic presure below 90 mm. of mercury systolic. A small decline in blood pressure was seen in almost every patient, but this was not considered significant. In the 100 patients in this study, hypotension below 90 mm. of mercury systolic was seen only in one during the operative period and in three during the postoperative period. All four responded promptly to small doses of vasopressor drugs, and the hypotension did not recur.

Electrocardiographic tracings were taken in five patients, and showed no variation from the normal record.

4. *Respiration*

Respiratory rate increased consistently in all patients receiving Viadril as an anaesthetic agent, while the tidal volume was decreased. Respiratory records

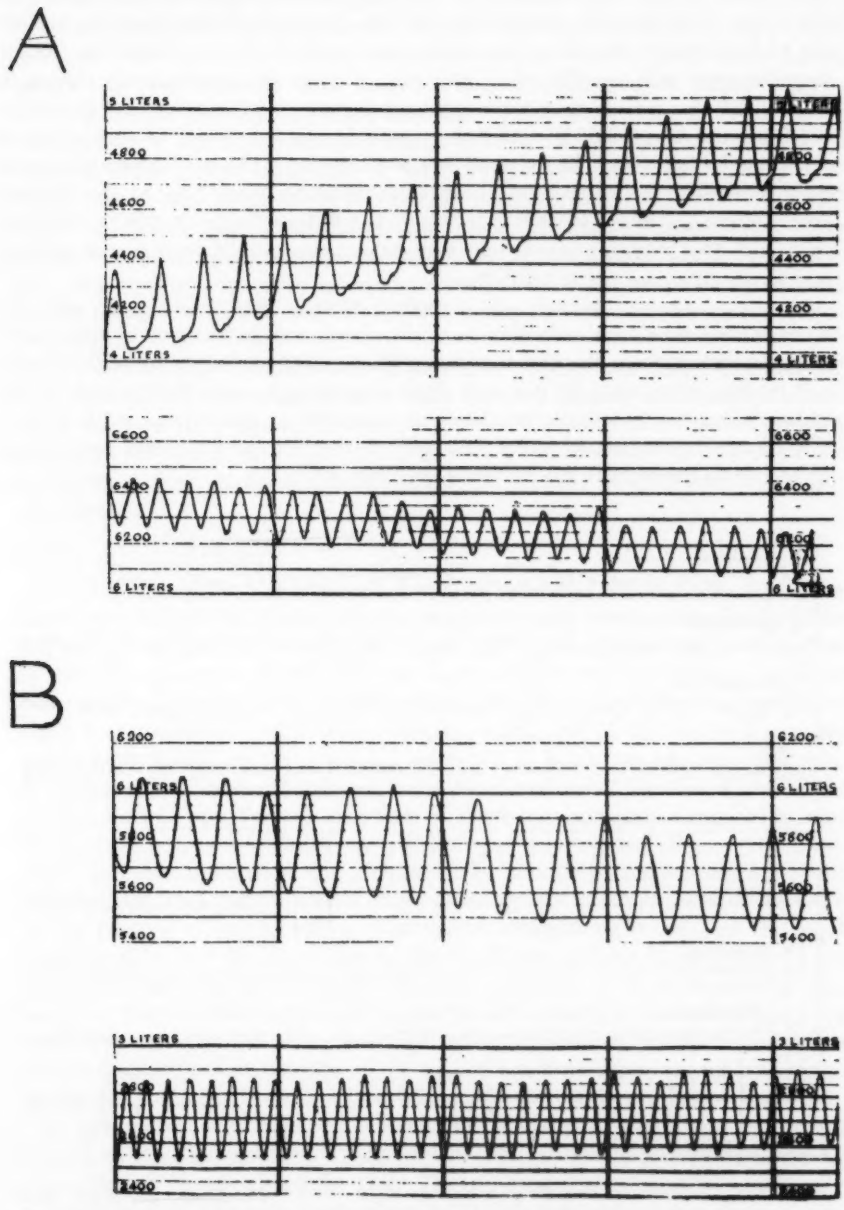

FIGURE 1. Respiratory records of two patients (*A* and *B*) during Viadril anaesthesia. The first line in each case is respiration at rest prior to induction, and the second a sample of the respiration at the deepest level obtained during the anaesthetic.

were made in five patients using a recording device applied to the exterior of the thorax, but this proved unsatisfactory for any purpose other than the recording of respiratory rate. Records were made for two patients with the Collins Respirometer, and samples of the records of these two patients are shown in Figure 1. The samples from the records of these two patients are designated in the figure as *A* and *B*. The first line in each case is the record of respiration at rest prior to induction. The second line is a sample of the respiratory tracing in each case after the patient had been established for some time at the deepest level obtained during the operation with Viadril anaesthesia. It will be noted in each case that the respiratory rate was sixteen per minute in the preinduction period, and the tidal volume 400 cc.

Minute respiratory volume was therefore 5400 cc. in each of these patients. Each patient showed a reduction in tidal volume and an increase in respiratory rate, the reduction in the first case being 50 per cent of the initial tidal volume, and in the second case 25 per cent. It is interesting to note that in case *A* the minute volume of ventilation was decreased to 4800 cc. per minute, while in case *B* it was greatly increased to 8400 cc. per minute. We are unable to explain this difference on the basis of the evidence available.

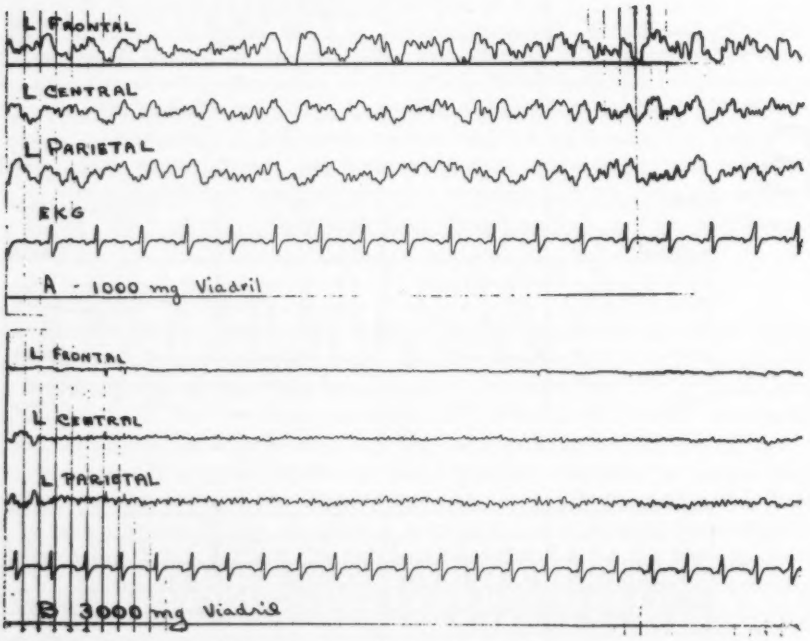

FIGURE 2. Electroencephalogram of a patient under Viadril anaesthesia. The upper record was made when the eyelid reflex was lost after 1000 mgm. of Viadril, the lower 50 minutes later after 3000 mgm. of Viadril.

5. *Electroencephalogram Studies*

Electroencephalographic patterns during anaesthesia have been reported by previous workers (7, 8). Electroencephalographic records were made for six patients in this series. In each one recording was commenced before injection of Viadril was started, and continued throughout the operation. The records obtained from these patients are comparable in all significant respects, and a representative record from one of these patients is shown in Figure 2. The upper record was made when the patient had lost the eyelid reflex after 1000 mgm. of Viadril. This record shows slow waves superimposed upon faster waves. There is normal ten cycle per second alpha rhythm visible, which is not seen in a patient who is naturally asleep or anaesthetized. This was the stage of anaesthesia which was found suitable in this series for operations such as uterine curettage.

As more Viadril was administered the total activity was decreased, and fifty minutes after the first record, when 3000 mgm. of Viadril had been given, and when the operation was well under way, there is a low voltage record which is shown in the lower record in Figure 3, with a fifteen cycle per second rhythm dominating. This is quite different from the records usually seen in surgical anaesthesia.

6. *Thrombosis of Veins*

Murphy *et al.* (6), Howland *et al.* (7), Taylor and Shearer (9), and others have reported the occurrence of venous reaction and venous thrombosis following the use of Viadril. Fourteen patients in this series showed venous thrombosis in the postoperative period, and six a perivenous reaction with no apparent occlusion of the vein. Two of the patients having postoperative venous thrombosis had received Viadril in a continuous infusion of 0.1 and 0.2 per cent respectively during rather prolonged operation. It would appear that other cases of postoperative venous thrombosis were associated with injection of the Viadril at such a rapid rate that the free flow of the intravenous infusion was impeded. In one case 2 per cent Viadril up to 1000 mgm. was injected into an intravenous drip running into a vein of the dorsum of the hand, with the intravenous tubing clamped off. This patient had a rapid development of thrombosis of the veins of the dorsum of hand, with a most severe oedematous reaction of the whole hand. In this case the circulation to the hand was so prejudiced that there was some fear that the patient might develop gangrene. It is of interest to note, however, that the hand appeared normal in all respects at the end of four days without treatment other than ice-bags in the immediate postoperative period, and at discharge from hospital at the end of ten days there was no evidence of venous thrombosis or reaction of any kind in the extremity.

In one patient who received a continuous infusion of Viadril 0.1 per cent in normal saline, a considerable quantity of the solution was injected into the subcutaneous tissues about the vein. This resulted in an immediate and severe reaction, having all the features of an acute inflammatory process. This reaction was completely dissipated by the interstitial infiltration of hyaluronidase solution,

and on the following day there was no evidence of perivascular reaction or thrombosis.

A number of patients complained of pain in the arm when the Viadril solution was injected somewhat rapidly. In the presence of a freely running intravenous infusion this pain disappeared promptly when the injection was slowed or discontinued. We have failed to establish any relationship between the occurrence of this pain during injection and the incidence of postoperative venous thrombosis.

7. *Postoperative Examination of Urine*

Since the occurrence of haematuria had previously been reported in dogs following the injection of Viadril (10), the urine of twenty patients who received Viadril for the operation of uterine curettage was examined after operation. In each case an indwelling catheter was placed in the bladder at the end of operation, and this was released at six hours and twelve hours. The urine samples obtained were examined for the presence of albumin and blood. In eight of these twenty patients a trace of albumin was found in the urine in the six-hour specimen. No patient had albumin in the twelve-hour specimen, and in no case was blood demonstrated in any specimen. The trace of albumin in the early specimens was considered to be due probably to the presence of the indwelling catheter.

8. *Reflexes*

We have confirmed the observation of Murphy *et al.* (6) and others (7, 9) that the pharyngeal reflexes are remarkably obtunded by Viadril in very light stages of anaesthesia. In many cases it was possible to insert a pharyngeal airway before loss of the eyelid reflex. Under light anaesthesia the pharynx and larynx could be readily inspected through a laryngoscope without sign of resentment from the patient. Stimulation of the larynx, however, or insertion of an endotracheal tube produced severe spasm. One patient had severe respiratory spasm during the recovery period following bronchoscopy.

9. *Endotracheal Intubation*

Intubation of the trachea may be readily accomplished under light Viadril anaesthesia when it is associated with adequate topical anaesthesia of the larynx and trachea. Sixteen patients in this series were so intubated, and we found relaxation of the jaws and pharynx to be quite adequate in each case. The intubation was as easily performed as if a relaxant had been used.

10. *Vomiting*

Postoperative vomiting was a very rare occurrence in this series. No patient vomited during the return of consciousness. Six vomited once during the first twelve postoperative hours. Of these one patient had acute appendicitis and had been vomiting for three days before operation; one had a post-traumatic cerebral syndrome associated with headache and vomiting, of many months' duration; one had a period of severe anoxia due to spasm following bronchoscopy, and one a similar episode following intubation at the end of a curettage, which was undertaken early in our series because we were unable to resist the tempta-

tion presented by the open relaxed larynx under light Viadril anaesthesia. Of the six patients who vomited, three did so only after taking food in the immediate postoperative period. No patient vomited more than once, and none after the first twelve hours.

11. *Headache*

Only four headaches were recorded in the postoperative period, and none of these were serious or significant. We believe that this incidence is probably no greater than it might be in a random sample of the same type of individuals who had had no anaesthetic or operation.

12. *Patient Reaction*

After operation, all patients in this series were entirely happy about their anaesthetic, despite the incidence of venous thrombosis. Many patients with experience of previous anaesthetics were definitely enthusiastic. The feature of their experience which appeared to impress the enthusiasts was the absence of diplopia, dizziness, or any sensation other than drowsiness during induction and recovery. Some patients who had previously experienced induction with a barbiturate agent were worried by the delay in going to sleep after the injection of the drug, but this was apparently forgotten after the operation.

Discussion and Conclusions

This study has demonstrated that Viadril produces satisfactory anaesthesia for a wide range of surgical procedures when combined with nitrous oxide and relaxants where these are indicated. In this respect it may be compared with the short-acting barbiturates and narcotics such as Demerol. Its tissue-irritating qualities and the slowness of induction tend to make it somewhat more cumbersome in practice than these other drugs. However, the extremely low incidence of complications other than venous thrombosis and the favourable patient reaction to the drug are factors which must demand serious consideration. It would appear from the experience of this study that Viadril may prove of value as a basal anaesthetic substance in some situations, such as the supplementation of regional anaesthesia, or for induction, but that the difficulty of control because of the long latent period between administration and maximum effect will make it less practical as an agent for general use throughout prolonged operations than other agents presently available to us.

Résumé

Les auteurs ont étudié, chez 100 malades, l'usage clinique du viadril (21-hydroxypregnanedione hemisuccinate de sodium). Le médicament est un stéroïde, fourni par la compagnie Pfizer, sous forme d'une poudre blanche instantanément soluble dans l'eau. Le produit est irritant pour les tissus et peut occasionner la thrombose des veines.

Au cours de cette étude, tous les malades ont reçu, en médication préopératoire, Demerol 100 mgm ou Morphine 1/6 gr. avec de l'atropine 1/150 ou 1/100. Le protoxyde d'azote et de l'oxygène, chez tous les malades, ont été administrés durant l'opération. Pour un curettage utérin, un dosage de viadril

de 5 mgm par livre de poids a suffi, mais, pour des opérations plus douloureuses, il a fallu donner 7.5 mgm par livre de poids. La liste des différentes opérations où le viadril a été employé comme anesthésique pour faire cette étude apparait en table I.

Avec le viadril, l'induction est lente. Le médicament doit être introduit lentement dans la tubulure d'une infusion intraveineuse au point de ne pas ralentir le rythme de l'infusion. Au cours de cette étude, la concentration de la solution de viadril était de 2 pour cent. Quand toute la dose de viadril est injectée en deçà de 5 minutes, le malade s'endort à peu près dans le même délai et ses réflexes palpébraux disparaissent en deça de dix minutes après le début de l'injection. Chez les malades où il fallait prolonger l'anesthésie, il a été difficile de maintenir une anesthésie égale à cause de cette période de latance entre l'injection du médicament et son effet maximum; toutefois, les auteurs ont trouvé que, si une dose égale à 50 pour cent de la dose initiale était injectée de nouveau au bout de 20 minutes et un dose égale à 25 pour cent de la dose initiale injectée à toutes les demi-heures par la suite, l'anesthésie était suffisante à condition d'y ajouter du protoxyde et, au cours des opérations où le relâchement musculaire est requis, des substances curarisantes. Au cours de l'induction, on n'a pas observé d'excitation, de vertiges, d'étourdissements ou aucun autre incident.

Les malades qui avaient reçu une seule dose de viadril pouvaient répondre à leur appel au bout de 20 minutes et après trente minutes, ils étaient tout-à-fait orientés. Chez les autres malades, de délai pour pouvoir marcher après l'arrêt du protoxyde d'azote a semblé varié de façon presque directement proportionnelle à la quantité de viadril donnée après la dose initiale.

Au cours de l'anesthésie au viadril, le rythme cardiaque s'est légèrement accéléré et, dans presque tous les cas, la tension artérielle s'est abaissée de façon peu marquée. Au cours de cette série de 100 malades, en une occasion seulement, la tension s'est abaissée au-dessous de 90 mm Hg au cours de l'opération et, en trois occasions, dans les suites post-opératoires.

Le rythme de la respiration s'est également accéléré de façon marquée chez tous les malades soumis au viadril, mais le volume de l'air courant diminuait. Des graphiques de la respiration de deux malades sont présentés en figure 2.

Les auteurs ont également fait des tracés électro-encéphalographiques chez six malades sous anesthésie au viadril. Chez les malades sous anesthésie légère au viadril, ils ont obtenu un rythme normal de 10 cycles par seconde, ce qui ne s'observe pas chez un malade dormant naturellement ou anesthésié avec d'autres agents. Chez les malades soumis à une anesthésie plus profonde (figure 3) le tracé est tout-à-fait différent de celui qu'on obtient habituellement au cours de l'anesthésie chirurgicale.

Au cours de cette série, quatorze malades ont souffert de thrombose veineuse et six autres de réaction periveineuse sans obstruction apparente de la veine. Il semblerait que l'apparition de la thrombose serait en fonction de la vitesse d'injection du viadril dans la tubulure de l'infusion, de sorte que l'infusion aurait été ralentie et même arrêtée. Un certain nombre de malades ont accusé des douleurs dans le bras lors de l'injection rapide du viadril.

Chez vingt malades qui avaient reçu du viadril pour subir un curettage utérin, les auteurs ont fait l'examen des urines au cours des suites opératoires. Chez huit

d'entre elles, ils ont trouvé des traces d'albumine dans l'échantillon prélevé par sonde six heures après mais aucune trace d'albumine dans l'échantillon prélevé 12 heures après l'anesthésie. Aucun malade n'a présenté du sang dans ses urines.

Sous anesthésie légère au viadril, les réflexes laryngés étaient abolis. Chez plusieurs malades, il a été possible de mettre en place un tube pharyngé avant même la disparition des réflexes palpébraux. Toutefois, une stimulation du larynx, à ce moment-à, provoquait un spasme laryngé. Chez 16 malades, l'intubation trachéale a été pratiquée facilement à l'aide de l'anesthésie locale du larynx et de la trachée.

Les vomissements post-opératoires ont été rares. Chez quatre malades, on a observé de la céphalée post-opératoire mais chez aucun d'eux elle n'a pris une certaine importance.

Au cours de cette étude, tous les malades ont manifesté, au cours des suites opératoires, une entière satisfaction au sujet de leur anesthésie; ceux qui avaient l'expérience d'anesthésies antérieures étaient réellement enthousiastes du manque de sensation au cours de l'induction. Les malades qui avaient l'expérience d'une induction antérieure aux barbituriques étaient parfois inquiets du retard à s'endormir.

Cette étude a démontré que le viadril peut produire une anesthésie satisfaisante pour une grande variété d'opérations si on l'associe au protoxyde d'azote et aux curarisants s'il y a lieu. Ses propriétés irritantes pour les tissus et sa lenteur d'induction le rendent difficile à manier, mais il semblerait que le viadril peut s'avérer utile comme substance anesthésique de base en certaines circonstances telles que en complément d'une anesthésie régionale ou pour une induction; toutefois, la difficulté de contrôler l'anesthésie à cause de la longue période de latance entre l'injection et l'effet maximum rend le viadril moins pratique comme agent d'usage courant au cours d'opérations prolongées que ceux que nous pouvons obtenir actuellement.

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CLINICAL STUDY OF PRESTONAL AS A MUSCLE RELAXANT IN ANAESTHESIA: A PRELIMINARY REPORT*

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IT is now over fourteen years since a relaxant drug was first employed in clinical anaesthesia (1). During this period of years, many different drugs have been introduced into anaesthesia because of their ability to relax skeletal muscles. Before considering the study of another such preparation, let us contemplate a few of the basic principles involved in an evaluation of new drugs in anaesthesia, as suggested by Melville (2).

I. *Effectiveness*

Is the drug really effective for the specific purpose for which it is being studied? Is it superior or inferior to the known agents used for the same purpose? In answering these questions, individual differences in susceptibility to drugs must always be kept in mind. A critical investigation of 10 or 20 cases, involving a more or less individualized and detailed study in each case, might be a more fruitful approach to the problem than a superficial and less critical study of 100 or 200 cases.

II. *Safety*

Is the drug free from injurious effects in the body?

III. *Dosage*

In making an evaluation, it is wise to start with minimal doses and gradually increase as the effects are observed. The intravenous method of administration is most easily controlled.

IV. *Influence of Other Drugs used in Anaesthesia*

"Combination" does not necessarily mean "potentiation."

During the last two years, Rudolf Frey (5) of Heidelberg, Germany, has studied various new drugs proposed as relaxants in anaesthesia:

(1) DESOXYDAURIZIN—*rejected* because of too weak action and too heavy histaminic side effects.
(2) PRAPARAT 9909—*rejected* because of depressive action on the respiratory centre.
(3) BELLADONNINBROMAETHYLAT—*rejected* because of central respiratory disturbances.

*Presented at the Annual Meeting of The Canadian Anaesthetists' Society, Mont Tremblant, P.Q., June 18-20, 1956.

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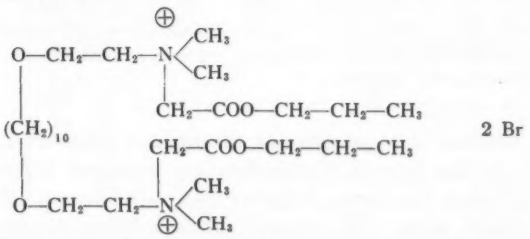
(4) Various other test preparations—*rejected* because of considerable increase in pulse rate.
(5) Dioxahexadekaniumbromid, PRESTONAL (Geigy)—*recommended.*

Frey has now used Prestonal in clinical anaesthesia in over 1000 cases, although less than a third of these cases have been studied in detail.

CHEMICAL PROPERTIES

The chemical formula for Prestonal has been outlined as follows:

N, N, N′, N′-Tetramethyl-N, N′-bis-(carbopropoxymethyl)-3, 14-dioxahexadecane-1, 16-diammonium bromide



Prestonal differs from the other such compounds in having a much longer chain between the two quaternary ammonium groups (molecular weight = 678.6). The substance is a colourless crystalline powder, easily soluble in water, with a melting point of 146°C. An aqueous solution is practically neutral, but at a pH of 7.4 and 37°C., Prestonal is spontaneously decomposed by hydrolysis to an extent of 50 per cent in 40 minutes. At a higher pH the half-life becomes shorter, at a lower pH, longer. Consequently, the J. R. Geigy Company of Basle, Switzerland, have prepared the product *Prestonal Geigy* (G 25, 178) in a 1 per cent solution, with 100 mg. in each 10 ml. ampoule (i.e., 10 mg. per ml.). This solution has been adjusted to a pH 3.2 approximately and has proven to be stable, even when stored for a considerable period.

When 50 mg. of this solution of Prestonal are mixed in a syringe with 375 or 500 mg. of 2 or 3 per cent thiopental respectively, a milky solution results. However, if this solution is left quietly on the table for a few minutes, it readily becomes very clear and is satisfactory for use.

HISTAMINE RESPONSES

Since some muscle relaxants are thought to release histamine in various degrees (3), simple observations were made on four of ourselves, using the method of small intracutaneous wheals. The amount and the speed of appearance of redness and induration were observed, using the following solutions:

1. Prestonal (10 mg. per ml.)
2. d-tubocurarine (3 mg. per ml.)
3. Succinylcholine (20 mg. per ml.)
4. Decamethonium (1 mg. per ml.)
5. N-saline

The results of these skin tests (see Table I) indicate that Prestonal and

TABLE I

SKIN SENSITIVITY TESTS (HUMANS)

	Subject A		Subject B		Subject C		Subject D		Average grade
	Wheal	Redness	Wheal	Redness	Wheal	Redness	Wheal	Redness	
I. Prestonal	4	6	5	5	4	6	5	5	5
II. d-Tubocurarine	4	3	3	4	4	4	3	4	4
III. Succinylcholine	2	2	1	3	2	2	2	3	2
IV. Decamethonium	1	2	1	1	0	1	1	2	1
V. Normal saline	0	0	0	0	0	0	0	0	0

Reactions were graded from 0 to 6, considering both the immediate and delayed responses, following small intracutaneous injections.

d-tubocurarine produce skin reactions of the highest order with Prestonal even exceeding d.T.c in this respect. Succinylcholine produced a reaction less than half that of the former two drugs, whereas decamethonium produced a positive result of the lowest order. The normal saline solution produced a negative response in all cases.

When decamethonium was first introduced into anaesthesia, this very low histamine response was hailed as one of its advantages over d.T.c. (4).

It was observed sharply by all our volunteers that intracutaneous Prestonal produced an immediate and somewhat prolonged "stinging" sensation and that succinylcholine produced a very mild and short "sting." Comparatively speaking, the other injections were painless. The acidity or the vehicle may be the cause of the "stinging" response.

CLINICAL STUDY OF PRESTONAL

Our clinical observations and impressions will, of necessity, be limited. We have used Prestonal as a muscle relaxant during anaesthesia for surgical procedures on only twenty-six patients.

In Table II the details of the cases are presented. It will be noted that the ages ranged from 14 to 78 years (see Tables II and III).

Of the 26 cases, 17 patients had abdominal surgery and thus required relaxation for major procedures both in the upper and in the lower abdomen.

Eight patients were postured in the Trendelenburg position for gynaecology.

As all of the patients (except one, who was undergoing bronchoscopy) were orally intubated by direct vision using a Macintosh laryngoscope, conditions for this procedure could be evaluated.

The anaesthetic agents and methods were quite uniform. Two per cent thiopental solution, in doses ranging from 100 to 500 mg., was used for induction in all cases and cyclopropane or nitrous oxide for maintenance.

Prestonal was given intravenously in various concentrations varying from 0.05 to 1 per cent solutions and of course in variable dosage, ranging from 40 to 265 mg. (see Table IV).

TABLE II

DETAILS OF PATIENTS RECEIVING PRESTONAL

Case No.	Patient	Sex	Age	Operation	Duration	Prestonal	Anaesthetics			Tensilon	Prestonal action		O.T. Intubation	Remarks
											Peak after first dose	Duration after last dose		
					Mins	Mg	Thiopental Mg	C_3H_6	N_2O	Mg	Mins.	Mins.		
1.	F.T.	F	27	Pelvic laparotomy	100	60+ 20= 80	200	Yes	—	—	3	50	Yes	
2.	C.E.	M	20	Laparotomy	90	50+ 10= 60	375	Yes	—	—	2.5	40	Yes	Bowel contracted
3.	N.S.	F	68	Cholecystectomy	120	50+105=155	320	Yes	—	—	3	40	Yes	Bowel contracted
4.	J.V.	F	30	Cholecystectomy	65	60+ 60=120	300	Yes	—	—	2	20	Yes	Bowel contracted
5.	W.M.	M	33	Excision of tumor in neck	120	60+ 40=100	300	Yes	—	—	3	—	Yes	Secretions moderate
6.	L.C.	M	22	Trauma— repair of face	120	80	500	Yes	—	—	3.5	—	Yes	
7.	J.T.	F	47	Hysterectomy	100	75+100=175	300	Yes	—	—	4	15	Yes	Cough 6′ after 1st dose
8.	A.C.	F	56	Hysterectomy (radical)	180	75+190=265	300	Yes	—	—	3	20	Yes	Note large dose
9.	J.K.	F	44	Hysterectomy	100	40+ 85=125	220	Yes	—	—	2	25	Yes	Bowel contracted
10.	D.S.	F	38	Mastectomy	60	40	300	Yes	—	—	3	25	Yes	

TABLE II

DETAILS OF PATIENTS RECEIVING PRESTONAL (*continued*)

Case No.	Patient	Sex	Age	Operation	Duration	Prestonal	Anaesthetics			Tensilon	Prestonal action		O.T. Intubation	Remarks
							Thiopental	C_3H_6	N_2O		Peak after first dose	Duration after last dose		
					Mins	Mg	Mg			Mg	Mins.	Mins.		
11.	W.H.	F	43	Hysterectomy	120	30+10+80=120	200	Yes	—	10	3	17	Yes	Difficult intubation
12.	S.T.	F	58	Appendectomy	60	40+20= 60	180	Yes	—	10+5	2	20	Yes	Tensilon—no effect
13.	F.S.	F	40	Diagnostic D & C	30	10+10+ 18+30= 68	100	—	Yes	10+10	2	12	Yes	Pulse from 124–80 (with Tensilon) very light anaesthesia
14.	M.S.	F	43	Hysterectomy	120	40+14+10+10 +10+40+20+20	240	—	Yes	10	3	30	Yes	Prestonal extravenously
15.	J.S.	F	48	Mastectomy	220	50	240	Yes	—	—	2	—	Yes	
16.	M.T.	M	74	Bowel anastomosis (CA)	90	20+20+20 +30=90	100	Yes	—	10+10	2.5	20	Yes	Anectine 40 mg. for intubation
17.	F.C.	M	30	Revision of leg amputation	30	50+50=100	320	Yes	—	—	3	10	Yes	Initial dose inadequate
18.	R.O.	M	14	Appendectomy	70	20+20+20=60	240	Yes	—	—	—	—	Yes	Anectine 50 mg. for intubation. Prestonal ineffectual. More Anectine.
19.	S.M.	F	61	Mastectomy	65	50	260	Yes	—	—	2.5	25	Yes	Reacted on tube

TABLE II

DETAILS OF PATIENTS RECEIVING PRESTONAL (*continued*)

Case No.	Patient	Sex	Age	Operation	Duration	Prestonal	Anaesthetics			Tensilon	Prestonal action		O.T. Intubation	Remarks
					Mins	Mg	Thiopental Mg	C_3H_6	N_2O	Mg	Peak after first dose Mins.	Duration after last dose Mins.		
20.	T.V.	F	26	Appendectomy	75	20+30+20 +30=100	260	Yes	Yes	—	—	60	Yes	Inadequate with small doses but later good
21.	M.G.	F	55	Cholecystectomy	80	50+30=80	220	Yes	Yes	—	3	30	Yes	
22.	A.W.	F	64	Mastectomy	80	60+20=80	160	Yes and Ethylene		—	3	4	Yes	Apnoea with cords still
23.	J.V.	F	38	Hysterectomy	120	60+60+40+ 60=220	240	Yes	—	—	3.5	30	Yes	Duration 2nd and 3rd dose 20 min. each
24.	J.O.	M	64	Bronchoscopy	20	50+20=70	200	—	Yes	10	4	20	No	Spontaneous breathing. Skin flush
25.	J.M.	F	33	Hysterectomy	110	50+20+10+ 15+30+30=155	240	Yes	—	—	4	20	Yes	Small doses inadequate
26.	J.W.	M	78	Resection of oesophagus	240	60	120	Yes	—	—	3	8	Yes	Bad risk (thoracotomy)

TABLE III

AGE DISTRIBUTION

Age	Number of cases
10—19 years	1
20—29 "	4
30—39 "	6
40—49 "	6
50—59 "	3
60—69 "	4
70—79 "	2
Total	26

TABLE IV

PRESTONAL: RANGE OF DOSAGE AND CONCENTRATION

Case No.	Intubation dose		Maintenance dose		Total dose Mg	Duration of operation minutes	Remarks
	Mg	Conc'n.	Mg	Conc'n.			
1	60	1%	20	1%	80	100	
2	50	1	10	1	60	90	
3	50	1	105	0.05	155	120	
4	60	1	60	0.05	120	65	
5	60+40	1	None		100	—	
6	80	1	None		80	—	
7	75	1	100	0.05	175	100	
8	75	1	190	0.05	265	180	
9	40	1	85	0.10	125	100	
10	40	1	None		40	—	
11	30+10	1	80	0.10	120	60	
12	40	1	20	1	60	60	
13	30	1	48	1	68	—	Special case
14	40	1	124	1	164	120	
15	50	1	None		50	—	
16	None		90	1	90	90	Intubated with Succinylcholine
17	50+50	1	None		100	—	
18	None		60	1		70	Succinylcholine before & after Prestonal
19	50	1	None		50	—	
20	20+30 +20+30	1	None		100	75	Initial doses inadequate
21	50	1	30	1	80	80	
22	60	1	20	1	80	—	2nd dose to cover light anaesthesia
23	60	1	160	1	220	120	
24	50+20	1				20	Bronchoscopy
25	50	1	105	1	155	110	
26	60	1	None		60	—	
AVERAGE	60		80		140	100	

Discussion of Results

1. *Conditions for Intubation*

It was consistently easy to obtain good conditions for intubation if an adequate dose was given. With doses of 30 or 40 mg. the jaw muscles and those of the pharynx might be adequately relaxed to expose the glottis but the vocal cords would be actively moving as spontaneous breathing was well maintained. If the upper respiratory passages were allowed to become obstructed, this spontaneous diaphragmatic breathing might cease and the patient appear apnoeic. This was demonstrated in a bronchoscopy case, where apnoea prior to the passage of the bronchoscope was followed by active diaphragmatic breathing during the examination. After the bronchoscope was removed, apnoea again occurred with momentary cyanosis, owing to upper respiratory obstruction. Thus upper respiratory paralysis occurred concurrently with *active* diaphragmatic breathing, in spite of doses of 50 mg. + 20 mg. (= 70 mg.) of Prestonal prior to bronchoscopy. This patient was reacting somewhat before his block had worn off but, on later questioning, remembered nothing before he was lifted onto his bed a few minutes later. The surgeon was pleased to have his patient breathing spontaneously during the examination.

In the average intubation case, a minimum dose of 60 mg. of drug produced good conditions for intubation. In most of these cases apnoea and maximal relaxation occurred 2 or 3 minutes after injection and lasted from 6 to 8 minutes more.

2. *Abdominal Relaxation*

In all but one of the abdominal cases it was possible to obtain good relaxation of the abdominal muscles, if an adequate dose, either singly or by rapid drip, was given. On the other hand, intermittent small doses of 10 or 15 mg., even if given repeatedly and at 3 or 4 minute intervals, might never produce good results. It seems that 30 or 40 mg. as the initial dose was necessary to obtain relaxation, whereupon additional doses of 20 mg. intermittently usually proved adequate for maintenance. This finding was comparable to what we have found with d.T.c.

The dose of Prestonal approximates about six times the dose of d.T.c which we were accustomed to use in similar cases.

3. *Pulmonary Ventilation*

To avoid the possibility of obstruction in the upper respiratory passages, an endotracheal tube is necessary. In addition the minimal amount of resistance to spontaneous ventilation is obtained. We could find no evidence of particular obstruction in the *lower* respiratory passages which might be considered to be spasm due to histamine-release. Such cases have been reported with d.T.c. but have been very rare in our experience with the latter drug.

Nevertheless, tracheal reactions from stimulation, such as mild cough or so-called "bucking on the tube" did occur fairly often. However, such responses are probably not related to histamine.

In most of our abdominal cases, good relaxation was associated with very

depressed ventilation. Usually controlled ventilation was established either manually, or automatically with the Jefferson Ventilator.

However, in a few cases, and especially if nitrous oxide was used instead of cyclopropane, quite adequate spontaneous ventilation was maintained during the period of relaxation. It was difficult to gauge the dose just right to provide such a situation. Possibly if more cases were handled with nitrous oxide, spontaneous ventilation might be more frequently obtained.

4. *Changes in Pulse and Blood Pressure*

In over 90 per cent of cases, the systolic blood pressure remained steady within a range of 10 mm. of mercury and the pulse variation was within ten points per minute.

In one case, the pulse rose from 80 to 110 per minute after 100 mg. of 1 per cent Prestonal had been given within one minute. It soon returned to normal. Similarly, in a patient in a very light stage of anaesthesia (after only 100 mg. of Thiopental) Prestonal, in a dose of 70 mg. within two minutes, resulted in an increase of pulse rate from 84 to 124. In this case, the pulse rate was readily reversed to 80 with Tensilon (10 mg. + 10 mg.).

Thus it is fair to say that a relatively large dose of Prestonal, with or without very light anaesthesia, may result in tachycardia which is probably due to a block of the cardiac vagal fibres, as occurs very frequently with gallamine (Flaxedil).

There were no cases showing hypotension after this drug but an occasional one showed a mild *transitory* rise in blood pressure.

If the drug is not given faster than 2 mg. per second, there will seldom occur any change in pulse or blood pressure.

5. *Period of Action*

The drug seems to reach its peak action after about two minutes, at which time apnoea usually appears. Occasionally relaxation seemed maximal three minutes after the 1 per cent solution was given into the intravenous tubing of a previously set-up infusion.

Although the duration of action of a single dose was difficult to evaluate, it appeared to be about six to eight minutes.

Nevertheless, after repeated doses or after dilute solutions were given by continuous infusion and then stopped, the period of apnoea lasted for a further 25 or 30 minutes. Thus there may well have been some cumulative effect. During this apnoeic period there is usually persistently good relaxation. Near the end of the period it is common to see tight spastic jaw muscles before the respiration is spontaneously resumed.

We have not seen cases of very prolonged apnoea with Prestonal, such as have been seen many times associated with the combination of pentothal, succinylcholine, and controlled ventilation.

6. *Antagonists and Mode of Action*

Frey (5) has reported several cases where the myoneural block of Prestonal was reversed or antagonized by 5 mg. of pyridostigmine, rather more effectively

than by neostigmine (prostigmine). However, neostigmine produced some antagonism. Thus he concluded that the block was probably of the antidepolarizing or competitive type. Recently, other investigators have challenged this idea and suggest that it is probably the "mixed block" type of relaxant.

On six occasions we have tried to reverse the action of Prestonal with Tensilon, using an 1/V dose of 10 mg., repeated in 5 or 10 minutes.

Although tachycardia, when present after Prestonal, could be reversed by Tensilon, we could not see any sharp reversal of the block. However, it did seem that the apnoeic period after the last dose of Prestonal was somewhat shortened. This may indicate some interference with the block and possibly a larger dose of Tensilon would have produced more conclusive results.

Thus our experience with Tensilon as an antagonist is not very convincing.

On two occasions we have intubated after thiopental and succinylcholine and then proceeded to give Prestonal for abdominal relaxation. With one patient—age 14—50 mg. succinylcholine had been used initially, and after 60 mg. Prestonal the relaxation was still very poor. Then an infusion of 0.1 per cent succinylcholine was turned on and immediately excellent relaxation was obtained. With the other patient—age 74—40 mg. succinylcholine had been used for induction. Prestonal in doses of 20, + 20, + 20 and 30 mg. was then given before relaxation was obtained and this patient was a thin elderly man with advanced malignancy in the stomach.

It thus appears that succinylcholine, initially, definitely interferes with the Prestonal block but that subsequent doses of succinylcholine are still effective. Thus one might think that the Prestonal block is not of the depolarizing type. Otherwise these two drugs would probably by synergistic.

Consequently, our bit of evidence seems to support the theory that Prestonal belongs to the "mixed block" type of relaxant. Clinically, it gives many of the responses which were seen after d.T.c.

7. *Other Observations*

(*a*) In no case did we see any muscle fasciculations after the injection of the drug, such as are commonly observed after injecting succinylcholine.

(*b*) In several of the cases for abdominal surgery, the small bowel appeared to be well contracted, which may often facilitate the surgical procedure. This observation has also been made after succinylcholine.

(*c*) In contrast to the frequent occurrence of excessive salivary secretions after certain other relaxants, the patients receiving Prestonal were usually notably dry.

(*d*) The condition of the vocal cords was usually not completely quiescent, and there occasionally followed a minor stimulatory reaction in the cords and trachea after the endotracheal tube was placed. This reaction was never troublesome.

(*e*) There was no evidence in our cases of intravenous or perivenous irritation following the injection of Prestonal in the various concentrations mentioned. In one of our cases, the site of the infusion needle in the arm, during a hysterectomy, was completely covered with drapes and was not only out of sight but out of reach. After a total dose of over 80 mg. of 1 per cent Prestonal in amounts

of 10 or 15 mg each, the relaxation was still very unsatisfactory. Only then was it found that the needle was dislodged and the drug as well as the infusion fluid was passing extravenously. The area was infiltrated with 1 per cent procaine and there were no ill effects whatever.

(*f*) We were not too surprised to find, at least occasionally, some histamine-like patchy flushing in the skin of the face, neck, and chest areas of some of our patients. This response was associated with the larger doses of 1 per cent Prestonal given within a short period of a few minutes.

Conclusions

1. Prestonal is capable of producing good relaxation of skeletal muscles.
2. The duration of relaxation after a single dose is relatively short, probably between 6 and 8 minutes, but periods of relaxation up to 30 minutes may follow repeated doses or continuous infusion.
3. The block appears to be of the mixed type, and thus antagonists are not convincing.
4. The method of breakdown of the drug has not been established although hydrolysis by enzymes has been suggested.
5. No serious undesirable side-effects have been found thus far.
6. Although much more experience is necessary to evaluate this drug, Prestonal has some advantages over the currently popular relaxants. Only time can tell whether such advantages will overbalance the disadvantages and thus create a place for this relaxant in anaesthesia.

Résumé

Les auteurs présentent un rapport sur l'usage du prestonal comme myorésolutif dans 26 cas. Ce médicament peut produire un bon relâchement des muscles striés. Après une dose unique, ce relâchement est d'une durée relativement courte, entre 6 et 8 minutes probablement, mais, si les doses sont répétées ou si la drogue est administrée en infusion continuelle, il peut exister des périodes de relâchement d'une durée allant jusqu'à trente minutes. Le type de blocage semble être varié aussi les antidotes ne sont pas efficaces. Les auteurs n'ont pas établi comment est métabolisé ce médicament, mais il semble qu'il serait hydrolysé par des enzymes. Jusqu'ici les auteurs n'ont pas, non plus, décelé d'effets indésirables.

Bien que, pour faire une bonne évaluation de ce médicament, il soit nécessaire d'en faire usage sur un nombre de cas beaucoup plus considérable, il est possible d'affirmer que le prestonal possède certains avantages sur les myorésolutifs employés couramment. Seul le recul du temps pourra permettre d'affirmer si ces avantages l'emporteront sur les désavantages et si ce médicament pourra se créer une place comme myorésolutif en anesthésie.

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CONSIDERATIONS CLINIQUES SUR L'EMPLOI DE DEUX NOUVEAUX CURARISANTS DE SYNTHESE: LE BREVATONAL ET LE MEDIATONAL

EUGENE ALLARD, M.D. et J. G. PATOINE, M.D.*

LE Brevatonal et le Médiatonal sont deux curarisants de synthèse mis sur le marché européen en 1952 mais encore très peu utilisés en Amérique du Nord, à notre connaissance du moins. Cependant, ils ont été le sujet de nombreuses recherches tant expérimentales que cliniques en Belgique, en France et en Italie.

Le Brévatonal est considéré comme un leptocurare bien qu'il ait une action plus tardive et plus prolongée que celle de la succinylcholine. Il a un temps de latence de 30 secondes à 3 minutes, une durée d'action de 20 à 30 minutes. Les phénomènes de curarisation passent par les étapes habituelles; il n'aurait ni effet central, ni effet histaminique, ni effet muscarinique si ce n'est de la sialorrhée et de la bronchorrhée occasionnelles qui apparaissent surtout à l'occasion des doses insuffisantes de curarisant. Il est dénué de toxicité et ne précipite pas lorsqu'on le mélange au penthiobarbital bien que l'on recommande de l'administrer isolément et quelques minutes avant le penthiobarbital afin de faire coincider l'action maximum de chacun si l'on doit pratiquer l'intubation. Il n'est pas cumulatif et on peut répéter l'administration de doses efficaces au besoin.

Le Médiatonal s'apparente chimiquement au Brévatonal mais il en diffère considérablement dans ses effets. Il semble tenir à la fois du curarimimétique et de l'acétylcholimimétique puisqu'il associe les caractéristiques de l'un et de l'autre. Ainsi, il potentialise les leptocurares, mais il possède certains effets neurovégétatifs à l'instar des pachycurares; et pourtant, selon la plupart des auteurs, la prostigmine le potentialise au lieu d'en réduire l'action. C'est pourquoi, à la suite de Brodowski et Huguenard, plusieurs auteurs le considèrent comme un curarisant intermédiaire unique. Nous pouvons résumer les caractéristiques cliniques du Médiatonal en affirmant qu'il est doué d'un pouvoir potentialisateur extraordinaire: il potentialise le thiobarbital fortement, les leptocurares à 300 pour cent et les pachycurares à 1000 pour cent. Il n'est pas toxique aux doses recommandées, soit à 30 à 40 mg. intraveineux pour l'adulte sain mais il est fortement cumulatif si administré à moins de 30 minutes d'intervalle. Ce pouvoir potentialisateur est mis à profit dans l'association Brévatonal-Médiatonal. En effet, on peut, selon cette technique, réduire très considérablement et la quantité et la fréquence des doses de curarisants et obtenir quand même un relâchement musculaire prolongé tout en déprimant très peu la respiration.

Depuis quelque six mois, grâce à la générosité de l'Union Chimique Belge, nous avons eu l'opportunité d'observer les effets du Brévatonal et du Médiatonal dans un petite proportion de nos anesthésies pratiquées à l'Hopital de l'Enfant-Jésus. Aux fins de la présente étude, nous avons revu sans sélection ni exclusion aucune nos 106 premiers cas.

La nomenclature de ces 106 cas (tableau I) représente assez fidèlement la

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proportion habituelle des interventions couramment pratiquées dans nos milieux, exception faite de certaines qui requièrent une technique particulière comme les césariennes, les interventions de neurochirurgie et beaucoup d'autres faites sous anesthésie rachidienne.

TABLEAU I

OPÉRATIONS

Cholécystectomies	14
Gastrectomies	4
Appendicectomies	23
Laparo-annexes, cottes, périnée	14
Hystérectomies	5
Resections intestinales	4
Herniotomies	4
Néphrectomies	3
Thyroidectomies	2
Plastie et stomatologie	10
Chirurgie oculaire	2
Abdomino-périnéale	1
Hémorrhoidectomie	1
Cystectomie	1
Luxation de l'épaule	1
Amygdalectomies	17
Total	106

Tableau II présente quelques détails sur les techniques suivies au cours de ces interventions. Dans tous les cas, nous avons pratiqué l'induction au Pentothal à la dose moyenne de 480 mg., après préparation préanesthésique au Nembutal ou Séconal, Démérol et Atropine. Nous avons utilisé le Brévatonal seul dans 65 cas, à la dose moyenne de 4.7 mg., le Médiatonal seul dans 13 cas à la dose moyenne de 19 mg. et l'association des deux dans 28 cas à la dose moyenne respective de 4 mg. et de 9.2 mg.

TABLEAU II

AGENTS ANESTHÉSIQUES ET CURARISANTS

	Nombre de cas	Dose max. mg.	Dose min. mg.	Dose moyenne mg.
Pentothal (Induction)	106	1000	100	480
Brévatonal	65	10	1.5	4.7
Médiatonal	13	35	5	19
Association				
Brévatonal	28	10	2	4
Médiatonal		20	3	9.2
N^2O+O^2	84			
$N^{20}+O^2$+éther	3			
$C^3H^6+O^2$	20			
O^2 seul	2			

L'anesthésique complémentaire a été le protoxyde d'azote et oxygène dans 87 cas et le cyclopropane-oxygène dans 20 cas et de l'oxygène seul dans deux cas.

Sans tenir compte de la durée des interventions ou du dégré de relâchement musculaire nécessaire, on constate dès maintenant que dans 81 pour cent des cas le protoxyde d'azote et oxygène associés à une très petite dose de Pentothal et aux myorésolutifs Brévatonal-Médiatonal, ont suffi pour maintenir une anesthésie adéquate.

Les appendicectomies, les amygdalectomies et les cholécystectomies (tableau III) sont les opérations ou nous avons le plus souvent employé le Brévatonal ou le Médiatonal et ceci pour deux raisons: (1) parce que ce sont là des interventions fréquentes; (2) parce que insensiblement, sans nous en rendre bien compte, nous avons eu tendance à utiliser le Brévatonal et Médiatonal, là où ils rendaient le plus service.

TABLEAU III

	Appendicectomies 23 cas			Amygdalectomies 17 cas			Cholécystectomies 14 cas		
	Dose en mg.			Dose en mg.			Dose en mg.		
	Min.	Moyenne	Max.	Min.	Moyenne	Max.	Min.	Moyenne	Max.
Brévatonal	1.5	3.8	9	3.5	4.8	10	5.	8	12
Médiatonal		20						30	
Association Brévat.	(1) cas	2					2	5.3	8
cas Médiat.		10					5	9	20
Pentothal	200	350	700	350	418	500	400	540	1000
Durée (min.)	20	37	49	20	29	40	65	90	170
Age	7	25	49	11	28	42	31	48	74
N^2O+O^2		20 cas			15 cas			8 cas	
$C^3H^6+O^2$		3 cas			0			6 cas	
Intubation	5 cas		21%	17 cas		100%	14 cas		100%
Respiration:		Durée max.			Durée max.			Durée max.	
Controlée	4 cas	17%	10 m.	4 cas	23%	10 m.	6 cas	42%	40 m.
Assistée	4 cas	17%	10	aucun			5 cas	35%	30 m.
Complications:									
Nausées et vomis.	8 cas	23%		3 cas	17%		5 cas	35%	
Cathétérismes	8 cas	23%		aucun			7 cas	5%	
Tachycardie, dyspnée avec température		1 cas							

Appendicectomies. Nous avons eu 23 appendicectomies dont l'âge varie de 7 à 49 ans (moyenne 25 ans) et la durée de 20 à 75 minutes (moyenne 37). Ils ont reçu de 200 à 700 mg de Pentothal (moyenne 350 mg), N^2O et O^2 dans 20 cas, C^3H^6 et O^2 dans 3 cas. Cinq ont été intubés soit 21 pour cent. Dans 20 cas sur 23 nous avons donné le Brévatonal seul à la dose de 1.5 à 9 mg. (moyenne

3.8 mg), dans 2 cas le Médiatonal seul à 20 et 25 mg. Une seule fois nous avons associé 2 mg de Brévatonal et 10 mg de Médiatonal.

Nous avons dû contrôler la respiration dans 4 cas soit 17 pour cent pendant un maximum de 10 minutes et l'assister dans 4 autres cas pendant un maximum de 10 minutes également. Dans les suites opératoires nous avons noté des nausées et vomissements 8 fois, de la rétention urinaire 8 fois et une fois une épisode de tachycardie avec dyspnée et hyperthermie qui a d'ailleurs régressé seule et qui est difficilement imputable à la curarisation.

Nous avons été impressionné au cours de ces appendicectomies du relâchement abdominal parfait sans dépression respiratoire importante; c'est une constatation qui contraste un peu avec ce que nous avons obtenu avec les autres curares et que nous semble digne de mention. L'unique fois que nous avons associé le Brévatonal au Médiatonal, association que nous jugeons maintenant superflue pour une appendicectomie, il nous a fallu contrôler la respiration pendant 10 minutes alors que l'opération en a duré 50. Il est également bon de noter que, malgré une prémédication plutot légère, une très faible dose de Pentothal associé au protoxyde d'azote a suffi pour des interventions dont la durée moyenne a été de 37 minutes.

Amygdalectomies. Nous avons fait 17 cas d'amygdalectomies en nous servant du Brévatonal pour l'intubation à la dose moyenne de 4.8 mg. La durée moyenne a été de 29 minutes. L'âge variait de 11 à 42 ans. Tous les patients ont été intubés après avoir reçu du Pentothal à la dose moyenne de 418 mg. et l'anesthésie a été complétée au protoxyde d'azote et oxygène. Nous avons contrôlé la respiration dans 4 cas, soit 23 pour cent pour un maximum de 10 minutes; 3 patients, soit 17 pour cent ont présenté des nausées ou vomissements dans les heures suivantes. Au cours des amygdalectomies, nous avons été frappés d'une part de la facilité de l'intubation, même après avoir administré la plupart de temps que la moitié de la dose de Brévatonal recommandée; d'autre part, du peu de dépression respiratoire. Le retour des réflexes est particulièrement précoce en fin d'intervention et le réveil est immédiat.

Cholécystectomies. Enfin, nous avons pratiqué 14 anesthésies pour cholécystectomies dont 5 au Brévatonal seul à la dose moyenne de 8 mg. (5 -12), une au Médiatonal seul à la dose de 30 mg. et 7 avec l'association des deux avec une moyenne respective de 5.3 mg. et 9 mg. Tous les patients ont été intubés. La durée moyenne a été de 90 minutes et 6 patients, 42 pour cent ont reçu une respiration contrôlée pendant un maximum de 40 minutes et 5 cas, 35 pour cent une respiration assistée pendant une durée max. de 30 minutes.

Dans les suites opératoires, 5 malades ont présenté des nausées ou vomissements et 7 ont du être cathétérisés.

Nous avons été vraiment étonnés de constater que l'atonie des muscles de l'étage supérieur de l'abdomen pouvait persister aussi longtemps avec une seule dose ou de petites doses répétées de Brévatonal que nous avons employé seul dans cinq cas. Les autres patients ont reçu une association de Brévatonal et de Médiatonal et aucune dépression respiratoire ne s'est prolongée au point d'assister le respiration jusqu'à la fin de l'intervention. La quantité de Penthothal a été relativement faible et l'anesthésie a été complètée au protoxyde d'azote dans 8 cas et au cyclopropane dans 6 cas.

TABLEAU IV

INCIDENCE RESPIRATOIRE

	Nombre de cas	Controlée			Assistée		
		Nombre	%	Durée	Nombre	%	Durée
Brévatonal	65	13	20	14	8	12.3	10
Médiatonal	13	1	7.7	15	3	23	25
Association Brévatonal Médiatonal	28	12	42.8	30	14	50	18
Total	106	26	24.6	20	25	24.5	18

Une étude de tableau IV nous permet de déduire que l'un ou l'autre de ces curarisants, employé seul, modifie peu la respiration mais que l'association des deux, même à dose très réduite, aboutit fréquemment à un arrêt respiratoire mais d'assez courte durée. Le chiffres de 20, 7.7 et 42.8 pour cent pour la respiration controlée et de 12.3, 23 et 50 pour cent pour la respiration assistée en sont des preuves évidentes. Cette brièveté d'atteinte des phénomènes respiratoires compense largement pour l'absence d'un antagoniste pharmacologique de ces deux produits.

Nous n'avons jamais observé de trémulations musculaires ou le tremblement caractéristique que l'on rencontre au moment de la dépolarisation avec le succinylcholine. Même si on injecte le Brévatonal avant le Pentothal, il est très rare que les patients se plaignent de sensation désagréable.

La sialorrhée pre-opératoire parfois rencontrée avec l'association des deux ne nous a pas semblé un inconvénient sérieux mais la forte incidence de rétention urinaire post-opératoire pourrait nous en faire restreindre l'usage chez les malades avec pathologie urinaire.

Pour ce qui est du Médiatonal seul, nous considérons qu'il a des indications très restreintes puisqu'il faut en administrer des doses très élevées pour obtenir un relâchement musculaire efficace. Par contre le Brévatonal occupe une place avantageuse entre les curares à action très brève et les curares à action prolongée. L'intubation est toujours facile, sans réflexes, avec une glotte béante moyennant que l'on attende 2 à 3 minutes avant de procéder.

L'association Brévatonal-Médiatonal, dans les interventions de moyenne et de longue durée, ne présente pas d'avantages appréciables sur les autres curares mais elle permet de réduire considérablement les doses respectives des curarisants et aussi des substances anesthésiques complémentaires.

En conclusion, nous ne saurions affirmer la nécessité du Médiatonal d'après le petit nombre d'observations faites mais par contre nous reconnaissons une place de choix au Brévatonal, en comblant une lacune de puissance et de temps dans la gamme des curarisants, pour les interventions de durée moyenne, toutes les fois qu'un effet myorésolutif s'impose soit pour intubation soit pour les opérations abdominales ou autres.

Summary

Brevatonal and Mediatonal are two synthetic curare-like preparations used in Europe since 1952.

Brevatonal belongs to the leptocurare group; but compared to succinylcholine its action is slower and more prolonged. Its latent period is from one to three minutes, and its average duration is twenty minutes. It combines with thiobarbital without causing precipitation, and repeated doses do not have cumulative effect.

Mediatonal has a rapid and prolonged action. It brings into play, by trigger action, changes in the electrical potential of thiobarbital, the leptocurares to the extent of 300 per cent, and the pachycurares 1000 per cent. It is non-toxic, but has a cumulative action if the doses are repeated within thirty-minute intervals.

The electrical potential mediator property is used in the Brevatonal-Mediatonal combination in order to reduce, to an appreciable extent, the dosage of the curare-like substance, as well as the anaesthetics.

We have used these preparations 106 times for various operative procedures. Special attention was given to their use in the more common types of operations, such as cholecystectomies, appendectomies, and tonsillectomies. There are certain features which are worth noting.

A depolarization block due to Brevatonal is never accompanied by much fasciculation, even when administered prior to Pentothal induction. Respiratory depression was never very marked in our experience; and intubation was never a problem. In our opinion, this relaxant, as a curare-like agent of relatively long duration, should occupy an intermediate place between succinylcholine and decamethonium.

With Mediatonal alone, satisfactory muscular relaxation can be obtained with a fairly large dose; the association of Brevatonal and Mediatonal, however, procures long anaesthesia with relatively small doses of the curare-like substance when complementary anaesthetics are used.

Brevatonal fills a gap in the duration pattern, between succinylcholine and the curare-like substances of longer duration; it is admirably suited for operations that are neither too long nor too short; and especially suitable when intubation or muscular relaxation are required.

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A NEW POTENT ANALOGUE OF NISENTIL

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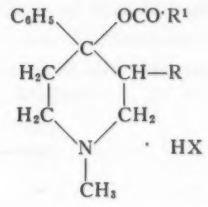
Previous work has shown that the diastereomeric 1,3-dimethyl-4-phenyl-4-propionoxypiperidines have powerful analgetic activity in experimental animals (1). The α-diastereomer, Ro 2-1196 (= alphaprodine hydrochloride = Nisentil ®^{HCl}), is less active (about equal to morphine in rats) but better tolerated than the β-diastereomer, Ro 2-1779, and was introduced commercially as a short-acting analgetic (2,3,4).

TABLE I

1-Methyl-3-substituted-4-phenyl-4-acyloxypiperidines



Compound Ro 2-	R	R¹	HX	M.P. (corrected)	AD_{50} (Intravenously in mice; mg./kg.)	LD_{50}
1196	methyl (α)†	propionoxy	hydrochloride	220–221	0.80	51.0
1779	methyl (β)†	propionoxy	hydrochloride	200–201	0.30	54.8
1932	ethyl* †	propionoxy	hydrochloride	230	0.74	45.0
7113	allyl (α)	propionoxy	hydrochloride	185–186	0.07	45.7
7839	allyl (β)	propionoxy	hydrochloride	202–203	0.26	53.0
7825	allyl (α)	butyroxy	hydrochloride	151–152	0.25	37.5
7826	allyl (α)	acetoxy	hydrochloride	211–212	0.45	67.5
7176	n-propyl (α)	propionoxy	hydrochloride	203–205	2.25	48.0
7142	dibromoallyl (α)	propionoxy	hydrochloride	182–183	1.36	53.0
7471	crotyl (α)	propionoxy	d-tartrate	95–97	28.40	57.5
7483	crotyl (β)	propionoxy	maleate	126–130	21.50	53.5
7482	n-butyl*	propionoxy	d-tartrate	140–143	20.00	41.5
7516	n-hexyl*	propionoxy	dl-malate	98–100	20.00	27.5
7994/1	benzyl*	propionoxy	hydrochloride**	207–208	24.0	39.0

*Relative configuration unknown—probably (α).

**Tested as dl-malate (water soluble, non-crystalline).

†Other pharmacological results published in (1).

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With the hope of obtaining compounds with qualitative and quantitative differences in analgetic potency, the structure was modified to obtain the 1-methyl-3-substituted-4-phenyl-4-acyloxy-piperidines described in Table I, which also presents the values of analgetic activity (AD_{50}) and toxicity (LD_{50}) of the compounds when administered intravenously to mice. Analgesia was assessed by mechanical compression of the tail. All compounds were tested in the form of racemates.

One of these agents, viz., Ro 2-7113 (1-methyl-3-allyl-4-phenyl-4-propionoxy-piperidine hydrochloride), while of the same order of toxicity as Ro 2-1196, was found to be considerably more active. The favourably high ratio between the 50 per cent lethal and analgetic doses is evident from Table II. In rats, Ro 2-7113

TABLE II

ANALGETIC ACTIVITY AND TOXICITY OF RO 2-7113 AND RO 2-1196 IN MICE, RATS AND RABBITS

Animal	Route	Compound RO 2-	AD_{50}* mg./kg.	LD_{50} mg./kg.	Ratio LD_{50}/AD_{50}
Mice	I.V.	7113	0.07	46.0	653.0
	I.V.	1196	0.80	51.0	63.8
Rats	I.V.	7113	0.05	13.4	268.0
	I.V.	1196	0.62	25.0	40.3
	S.C.	7113	0.13	80.0	615.4
	S.C.	1196	1.00	50.0	50.0
	P.O.	7113	12.0	125.0	10.4
	P.O.	1196	21.0	90.0	4.3
Rabbits	I.V.	7113	.06	7.8	130.0
	I.V.	1196	2.0	22.0	11.0

*Calculated in mice and estimated for rats and rabbits. For latter species, doses represent those required to prolong reaction time 100 per cent.

exhibited a high order of analgetic activity when measured by a modification of the Ercoli and Lewis technique (5). The ratio between toxicity and analgesia was greater than that of Ro 2-1196 when the drugs were given intravenously, subcutaneously or orally. In rabbits, comparable results were obtained by the intravenous route of administration, although equivalent degrees of analgesia were associated with similar degrees of respiratory depression when studied by combining the Ercoli and Lewis technique for measurement of analgesia and the Wright technique (6) for measuring minute volume exchange. Significant analgetic effects were also demonstrated in the dog.

Clinical trials with Ro 2-7113 were carried out on a limited scale by the oral and intravenous routes. Thirteen ambulatory patients with inoperable malignancies received alternately 2 to 6 mg. Ro 2-7113 or levorphan. The drugs were administered orally, 4 to 8 hours apart, for periods ranging from 4 to 97 days. The onset, duration, and degree of analgesia and the incidence and severity of

side effects were recorded following the use of both compounds. A comparative analysis of results could not be made because of the progressive nature of the underlying pathology. However, the impression was gained that the onset, degree, and duration of action of identical oral doses of Ro 2-7113 and levorphan were quite similar. The incidence of side effects such as drowsiness, vertigo, and nausea was usually lower and the severity less marked after the administration of Ro 2-7113 than after levorphan. Administered intravenously on a weight basis, Ro 2-7113 was found to be 2 to 3 times, 10 times, and 25 to 30 times more potent than morphine, alphaprodine, and meperidine, respectively. By this route, the duration of action of Ro 2-7113 and alphaprodine was approximately equal. As with other potent narcotic analgetics, large doses of Ro 2-7113 produced marked respiratory depression which was readily antagonized by levallorphan.

Ro 2-7113, in combination with levallorphan, was used intravenously for supplementation of N_2O–O_2 anaesthesia in 230 patients. The initial dose of Ro 2-7113 was 0.1 mg./kg. and that of the narcotic antagonist, 0.02 mg./kg. The anaesthetic management (7) was the same as that used for 852 patients who received 1 mg./kg. of alphaprodine and 0.02 mg./kg. of levallorphan as initial doses. In these two series, the effects of Ro 2-7113 and of alphaprodine were identical for all practical purposes.

The preliminary observations here reported suggest that Ro 2-7113 may become a clinically useful analgetic.

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AN EVALUATION OF LOCAL AND GENERAL ANAESTHESIA FOR DIAGNOSTIC BRONCHOSCOPY*

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The subject of anaesthesia for bronchoscopy has been ventilated with great frequency and at considerable length for many years. It is evident that there are many ways of performing this feat and that, since papers are still being written on the subject, 100 per cent success has yet to be achieved.

This paper is based on work carried out, at the Brompton Hospital for Diseases of the Chest, London, England, on 275 diagnostic bronchoscopies; 145 of these patients received local and the remainder general anaesthesia.

It is proposed to present this subject under the following headings: (1) A discussion of the ideal anaesthetic conditions for bronchoscopy; (2) A report and discussion of the degree of success—or lack thereof—achieved by both local and general anaesthesia in the present series; (3) Suggestions as to how current methods of anaesthesia may be improved upon, in the not too distant future.

It is noted that the literature on this subject gives very few figures for certain aspects of this problem—especially patients' opinions, surgical facility and complication rates. It is hoped that, to some extent, this paper may fill the gap.

Ideal Anaesthetic Conditions

As in other fields, a search is being made for that form of anaesthesia which will produce ideal operating conditions with a minimum of unpleasantness for the patient.

A. *Ideal Operating Conditions*

Relaxation of the jaw is an essential in this procedure and it is necessary to be able, without trauma, to insert the bronchoscope between the vocal cords. However, two other necessities are open to discussion:

(1) Respiratory movements. These permit the surgeon to observe two things: (*a*) Vocal cord mobility—this is something which may be assessed separately by indirect laryngoscopy; (*b*) The respiratory constrictive movements of the bronchial orifices, lack of which denotes pathology in the immediate vicinity. Knowing that this lack of mobility is associated with recognizable increased local rigidity, not dependent upon respiration, most bronchoscopists are prepared to forego the opportunity to assess this point.

(2) Cough reflex. It is important to prevent the patient coughing as a result of the irritation of the bronchoscope but he should be in control of his more bulky secretions and, more so, of any gross bleeding produced during the examination. Really extensive local anaesthesia abolishes the cough reflex but the

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, Mont Tremblant, P.Q.

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wakeful patient can still cough voluntarily as can the patient under general anaesthesia who has had no local anaesthesia and who can be wakened very quickly. The majority of the patients under general anaesthesia in this series received such a sequence and its merits and demerits will be discussed later.

At this point, it should be stated that many very experienced bronchoscopists are most concerned at the difficulty of saving the life of the patient under general anaesthesia who suffers a massive haemorrhage owing, for instance, to inadvertent pulmonary artery puncture at biopsy. The resulting gush of blood is an extremely alarming sight but the situation is, by no means, irreversible. Dylwyn Thomas (1), from Sully, reports that he has experienced such an incident under both types of anaesthesia and the increased difficulty of having a patient under a general anaesthetic was very troublesome. d'Abreu (2) recommends that, in the event of such a catastrophe, a Thompson bronchial blocker be inserted down the bronchoscope (which should have been kept in position) thus confining the haemorrhage to one lobe or lung.

B. *Degree of Risk*

The danger of haemorrhage has been mentioned. Other points of more constant importance are:

(1) Ventilation. Of necessity, many of the candidates for this examination will have gross pulmonary disease and no patient should be anaesthetized for bronchoscopy until his chest plates have been examined by the anaesthetist. Failure to be aware of the presence of a large fluid level in an empyema cavity with a bronchopleural fistula, for instance, could terminate in a serious emergency.

Good spontaneous respiration, through a bronchoscope down which oxygen is flowing and which has several lateral orifices, should ensure adequate oxygenation and carbon dioxide elimination. Under local anaesthesia, this is usually the case. Under general anaesthesia, it is unfortunate that spontaneous respiration, absent cough reflex and complete wakefulness within a minute or two of the end of the examination are difficult to achieve. One of these is usually sacrificed. It is felt that general anaesthesia is only acceptable for bronchoscopy if the endoscopist can complete his task easily and if the patient is completely awake within a minute or two of the end of the examination. The postoperative somnolent patient, locally anaesthetized, is in a most unsatisfactory condition to look after his secretions. If the local has achieved its intended effect then, of necessity, a conscious effort will be necessary for expulsion of secretions. Thus, local and general should not, in the author's opinion, be combined. In order to achieve the above requirements with drugs presently available, it is common—as in this series—to use a short-acting relaxant to the point of gross or complete diminution of respiratory movements. It is felt that hypercarbia is the main risk of this technique, given hyperventilation with oxygen at the outset and an adequate flow of oxygen, delivered at carinal level during the examination. This is borne out, in respect to those with reasonable pulmonary function, in the very interesting report by Jooste (3) in which he described cases rendered apnoeic and not ventilated for

considerable periods. In one example, he gives blood gas figures after thirty minutes' apnoea. At this time, the oxygen saturation was 103 per cent but the arterial pH was 6.97, the carbon dioxide tension having risen to nearly three times normal! There were no clinical symptoms or signs other than fifteen points rise in systolic blood pressure. He reminds us of the insufflation methods introduced by Meltzer and Auer, but points out that the very high flow of oxygen necessary to eliminate carbon dioxide is impracticable in this type of work. This will be referred to again in the report of the cases under general anaesthesia. The introduction of a small catheter, through the glottis and down to the carina, prior to passing the bronchoscope alongside it, enables oxygen to be delivered at the optimum point. This method is in use in many centres and was described by Cheatle and Chambers (4) in 1955. Ventilation, in the apnoeic patient, may be assisted by routine manual compression of the anterior chest wall, and, in an emergency, by inserting a sawn-off endotracheal tube (connected to a rebreathing bag and oxygen supply) into the end of the bronchoscope. These methods of ventilation were used in this series and have been described elsewhere (5, 6). Herron (8) has described an adaptor which may be placed over the surgeon's end of the bronchoscope. This has a transparent window in it, occluding the end of the bronchoscope and enabling more adequate ventilation to be achieved as the examination continues. The window may be hinged back to permit passage of telescopes and forceps. In passing, it is worth stressing that the anoxic collapsed patient will have a lax glottis and inflation will be difficult owing to leak of gas—just as it is with an uncuffed endotracheal tube.

(2) Toxic reactions. The literature is scattered with reports of toxic reactions to local anaesthesia and, although those concerned now have an increased awareness of the maximum dosage of the relevant agents, fatalities still occur. In the fourteen years prior to this series, two deaths had occurred at the Brompton Hospital in association with bronchoscopy, both due to toxic reactions to local anaesthesia. In this series, one cardiac arrest occurred following amethocaine administration but this was reversed by prompt massage. In the fewer years that general anaesthesia has been in use at this hospital, no deaths had occurred up to the time of writing.

C. *Unpleasantness for the Patient*

No figures were found in the literature referring to the patient's opinion on which type of anaesthesia he would prefer after experience of one or both forms, although many authors suggest that general is usually preferable (5, 6, 7). In this series, 145 patients received local anaesthesia. All our patients were asked, the next day, if they would rather have a general anaesthetic if the procedure had to be repeated. Of these, 69 said "yes" (47.6 per cent). Several more said they did not know, because they had never had a general anaesthetic. Of 130 patients given general anaesthesia, 120 said they would have the same again. The remaining ten had experienced local anaesthesia previously and, of these, nine were adamant that they would never have bronchoscopy done under local again (to the extent of wanting to know why they had not had a general anaesthetic previously!). The remaining patient (0.8%) said he had had a nasty dream

with the general anaesthetic (which he could not remember the next morning) and would rather have a local.

Thus, in this series, 47.6 per cent of those given locals would prefer a general next time and 0.8 per cent of those given general anaesthesia would prefer a local.

Techniques

(1) Local anaesthesia. It is not proposed to go into detail on the many methods and drugs used for this type of work except to say that 100 per cent efficiency (i.e. the patient so anaesthetized that the bronchoscope may be slipped through the open glottis, an examination and, if necessary, a biopsy completed and the bronchoscope withdrawn—all with no reaction, as can be achieved with general anaesthesia) is almost impossible to obtain without paying most meticulous attention to every detail of the procedure: initial premedication, supplementation of this intravenously, application of the local anaesthetic, and accompanying encouragement of the patient. From the time the patient arrives in the preparation room, to the time he is ready for bronchoscopy, at least twenty to thirty minutes will have elapsed. One must be prepared to reapply the local if the first application was inadequate. To do this one must either have a very large staff and appropriate sausage-machine administration, as in the one or two world-famous bronchoscopy clinics in the United States, or one must have all the time in the world. Under such circumstances, nearly every anaesthetist will be 100 per cent successful. Unfortunately, where a row of bronchoscopies is to be done, such circumstances seldom prevail and it appears that it matters little which technique of application of local anaesthesia one uses, provided one is well acquainted with one of them.

(2) General anaesthesia. Very good descriptions of technique are in the literature (9, 5). The requirements of general anaesthesia for this examination have been outlined when discussing some of the risks involved. The technique used in this series will be described in association with the results achieved.

Brompton Hospital Series

The patients in this series were in a specialist thoracic hospital and displayed a wide range of pulmonary pathology. The distribution of types of case given local or general anaesthesia was very similar. Gross pathology existed in approximately equal numbers, in both groups.

Cases were assigned to one or other type of anaesthesia solely on the grounds of surgeon's preference; i.e. certain surgeons were in the habit of bronchoscoping all cases under local. Others were prepared to examine all cases under general anaesthesia, subject to the anaesthetist's approval. Broadly speaking, patients were not assigned to one or other group, in this series, on the grounds of their pathology but contraindications to each form of anaesthesia will be considered later.

Only certain aspects of the two groups bear comparison and it was decided that it would be unwise to bronchoscope alternate cases under local and general anaesthesia since it was noted, very early on, that the bronchoscopist accustomed

to one type of anaesthesia was not necessarily adept and happy with the other type. Thus, an acknowledged expert at passing a bronchoscope under local anaesthesia—with a "tight" pharynx—was noticeably less dexterous when inserting the instrument through the lax oro-pharynx under general anaesthesia. It was considered sound to compare the figures for several surgeons, each using the method with which he was most familiar. Some of the cases were examined by registrars, whose dexterity had not become specialized in relation to any one type of anaesthesia.

Two clinical features were considered a basis for comparison of the two groups, as a rough assessment of the extent of respiratory disability. These are shown in Table I. It will be seen that for practical purposes the two groups are very similar but it should be mentioned that, in some instances, the decision as to which group was correct for a given case was difficult—especially with regard to sputum volume.

TABLE I

DYSPNOEA	L.A.	G.A.
No dyspnoea	61 (42.1%)	52 (40%)
Dyspnoea on exertion	76 (52.4%)	72 (55.4%)
Dyspnoea at rest	8 (5.5%)	6 (4.6%)
SPUTUM	**L.A.**	**G.A.**
Trace or less	69 (47.6%)	71 (54.6%)
Less than 2 oz.	70 (48.3%)	54 (41.6%)
2 oz. and more	6 (4.1%)	4 (3.1%)

The age distribution in the two groups was even, being from 18 to 78 under local and 14 to 77 under general anaesthesia. Younger patients, bronchoscoped under general anaesthesia, were not included.

Difficulty in Instrumentation

If the surgeon was unable to insert the bronchoscope at the first attempt and without hesitation, this was classed as difficulty. Thus, 39 of the cases with local anaesthesia (i.e., 26.9 per cent) proved difficult and 18 (i.e., 13.8 per cent) of those under general anaesthesia.

Length of Bronchoscopy

Each examination was timed from the moment the surgeon advanced on the patient with the bronchoscope to the moment it was removed from the mouth. These times were grouped into three-minute periods and the results are shown in Table II. A higher percentage of cases under general anaesthesia was completed in nine minutes.

Thus, it is seen that, in this series, it was somewhat easier to pass a bronchoscope under general anaesthesia and the whole examination took less time—especially when one considers the greater speed of induction of general, as

TABLE II

Length of examination	L.A.	G.A.	L.A. % age	G.A % age
0-3 minutes	9	21		
4-6 minutes	38	44	57.3%	76.2%
7-9 minutes	36	34		
10-12 minutes	29	20		
13-15 minutes	22	6	42.7%	23.8%
More than 15 minutes	11	5		

opposed to local, anaesthesia. Having said this, it is necessary to know whether the longer time taken to do a bronchoscopy under local anaesthesia is due to the additional care and, consequently, gentleness necessary and whether these cases have fewer sore throats and damaged mouths after operation as a result of this care.

Sore Throats and Damaged Mouths

Figures for these complications, due to trauma, are shown in Table III. It can be seen that no reduction in trauma resulted from the increased time taken to do the examination under local anaesthesia and, in fact, there was more trauma with this form of anaesthesia. It should be stressed that none of the bronchoscopists using general anaesthesia felt that their examination was unduly hasty as a result of any feeling of urgency.

TABLE III

	L.A.	G.A.
Sore throats	122 (84%)	97 (74.6%)
Sore lips and gums	10 (6.9%)	2 (1.5%)

Efficacy of Local Anaesthesia

If one accepts the fact that, under general anaesthesia, near perfect operating conditions can be provided—in terms of respiratory quiescence—it is pertinent to consider to what extent local anaesthesia will provide the same facilities. The members of the staff of this hospital used variations on the theme of administration of local anaesthesia. Cocaine, Amethocaine, and Xylocaine were all in use. Swabbing of the piriform fossae, using Krause's forceps, dripping local anaesthetic on the glottis from a Nelson's syringe and curved cannula, and injecting local anaesthetic through the crico-thyroid membrane were all used, in various combinations. Omnopon and Scopolamine was the usual premedication. Luminal was added to this on some occasions. Intravenous Demerol was given, prior to the examination, in some cases where patients appeared inadequately sedated.

Agreeing with Rubin and Kully (10) in their excellent paper on topical anaesthesia for bronchoscopy, the author believes that variations in technique are of little importance, there being many ways of anaesthetizing a larynx but no substitute for meticulousness with the method of choice.

The results of the locals given in this series were grouped as follows: (1) Good. This indicated no difficulty in instrumentation, no reflex response, and a quiet patient. (2) Moderate. Only the 100 per cent perfect anaesthetic was put into the "Good" group and anything short of that (e.g., one or two bouts of coughing) was termed moderate. (3) Bad. This meant that there was a shambles where the bronchoscopy was only completed with some difficulty (e.g., difficult instrumentation with phonation, coughing, and head moving).

The figures in each group are seen in Table IV. Thus, 87 per cent of cases were reasonably good but the majority were not perfect.

TABLE IV

Efficacy of Local Anaesthesia	
Good	29 (20%)
Moderate	97 (66.9%)
Bad	16 (11.0%)
Converted to General anaesthesia	3 (2.1%)

It should be stressed that, broadly speaking, difficult cases were not moved from the local to the general group and that a higher percentage of good results might have been achieved with local anaesthesia had more time been given to each case. However, it is considered that these figures are representative of the results achieved in the average busy unit, where a serious attempt is being made to obtain efficiency in the limited time available.

General Anaesthesia

It is evident, from the foregoing discussion, that general anaesthesia is preferable with a high percentage of patients and permits a quicker and easier examination, with less trauma, than is the case with local anaesthesia. It is, therefore, necessary to know whether one can recommend its more universal use for this type of endoscopy. The answer will depend on whether it produces any other side-effects and whether these are more severe than those produced by local anaesthesia. Complications, not caused by trauma on instrumentation, are shown in Table V.

TABLE V

Further complications	L.A.	G.A.
Postoperative vomiting	11 (7.6%)	19 (14.6%)
Headache	1 (0.7%)	3 (2.3%)
Painful eye (corneal abrasion)	0	1 (0.8%)
Peri-venous haematoma	0	2 (1.5%)
Cardiac arrest	1 (0.7%)	0
Muscular pain	0	30 (23.1%)
Pulse irregularity		26 (20%)
Prolonged apnoea (8 minutes)	0	1 (0.8%)

Complications

It is apparent that, apart from the results of trauma, more complications follow the use of general anaesthesia.

Cardiac arrest. The one case of cardiac arrest was due to a trainee thoracic surgeon being somewhat over-enthusiastic with his dosage of Amethocaine, in a diminutive patient. Interestingly, this patient was one of those given luminal gr. 3 orally, as an anticonvulsant, in addition to Omnopon and Scopolamine. Thiopentone sodium, intravenously, arrested convulsions and permitted intubation. Prompt thoracotomy and cardiac massage were effective and the bronchoscopy was performed a few weeks later, under general anaesthesia. It is felt that, while everyone has a maximum dosage for local anaesthetic agents in mind, there is always someone who, not having seen a toxic reaction, is inclined to be too liberal with the drug, and eventually learns the hard way.

Muscular pains. Subcostal pain, following the administration of succinylcholine, was reported and discussed by Currie (11) and others. Since then, this has become recognized as a very frequent occurrence. Typically, the day following anaesthesia the patient feels stiff (as though after unaccustomed exercise). This stiffness becomes increasingly painful, reaching a peak that night and passing off by the following night. The aching may affect any part or all of the body. Those affected most are: (1) Those least accustomed to physical exercise: thus, elderly ladies will occasionally be completely incapacitated for 36 to 48 hours; small children are least affected—although none seems immune. (2) Those receiving a big dose quickly. It has been suggested, by Churchill-Davidson (12), that another relaxant will markedly diminish this problem. Hegarty (13), in a very recent review of the subject, states that "combining a second depolarizing muscle relaxant with suxamethonium chloride does not increase the incidence of pain and may decrease it." It is the author's opinion that this mixing of relaxants overcomplicates an already thorny subject and is to be deprecated. Early ambulation is said to increase the incidence of this complication. Churchill-Davidson (12) quotes 66 per cent incidence in the early ambulants, in his series, and less than one quarter of this in patients confined to bed. It is probable that the figure in the present series is artificially low since the majority were discharged from hospital on the first postoperative day. These would be questioned at about the time of the onset of the symptoms and before they reached their peak.

Pulse irregularity. Twenty-six patients under general anaesthesia were observed to develop irregularity of the radial pulse, usually preceded by bradycardia. These were reversible either by the resumption of spontaneous respiration or by artificial ventilation with oxygen. It is of interest that cyanosis was only observed in four of these cases and it is thought that, while anoxia may have played a part, the more significant feature was hypercarbia. E.C.G. records were taken in a few instances but these patients responded with sinus rhythm! This incidence of cardiac irregularity is considered to be of the greatest significance. It is highly probable that the irregularity was due to ventricular extrasystoles. Unfortunately, no recommendation can be made as to which cases are likely to show this irregularity. In this group with arrhythmias, the youngest

patient was twenty-six and the oldest seventy. None had dyspnoea at rest, eight had no dyspnoea, nine had no sputum, and only one was producing more than two ounces daily. The pathology present in these patients was no more severe than in the remainder of the series.

Recovery

There remains the question of whether the patients given general anaesthesia are as able to look after themselves, immediately after operation, as those under local anaesthesia. The advantages of general anaesthesia would be completely offset if they were in increased danger after operation.

Of the patients given general anaesthesia, 115 (i.e., 88.4 per cent) were awake within five minutes of the end of the examination and able to answer to their name. Three were awake within fifteen minutes, 2 within half an hour, and 10 took longer than this. The 15 patients who did not wake up within five minutes will be analysed.

One became anoxic during the bronchoscopy. He had severe chronic bronchitis and emphysema with exertional dyspnoea. This case came early in the series and it is thought that further experience with the technique would have prevented this. Interestingly, the patient's pulse was regular throughout.

Five patients, on arrival in the operating room, were found to be over-sedated on their premedication.

Nine patients were given a large dose of thiopentone, in an attempt to ensure there was no possible recollection of the end of the examination. The intention was to reverse this with Megimide (N.P. 13). However, the latter drug was of no value whatsoever in this respect (as reported elsewhere (14)).

In order to achieve quick awakening at the end of bronchoscopy, and to avoid a period of sedation punctuated by coughing and spasm after operation, it is necessary to reduce the induction dose of thiopentone to that which will just abolish the eyelash reflex. Approximately 50 mgm. succinylcholine is given immediately and the patient is hyperventilated with a high flow of oxygen, after the fasciculations with associated vocal cord adduction have passed. Bronchoscopy is performed with oxygen flowing down the bronchoscope and rhythmical manual compression of the chest is commenced immediately. The apex beat or radial pulse must be observed closely. Movement is an indication for more succinylcholine, as is the first sign of diaphragmatic excursion—provided the pulse is regular and the colour good. Unless the examination is unusually prolonged, no further thiopentone is given.

As might be imagined, a proportion of patients vaguely remember the end of the examination. One must accept this if all patients are to awaken quickly after operation. In this series, on direct questioning, 40 patients remembered something (30.8 per cent). The majority of these were not sure whether they had been aware of anything or not and said they would not have mentioned it had they not been asked. One dreamed he had his pipe in his mouth! Seven of the 40 considered this experience unpleasant but not sufficiently so to rule out a general anaesthetic on another occasion. None was warned previously that

this might happen. Several proformata were marked, to show which patients might have been awake during the examination, and it was interesting to note that there was little relationship between clinical impression and actual fact! The most purposeful of movements occurred in patients with no recollection of anything.

Possible Improvements on This Method of General Anaesthesia

A limited trial of the ultra-short-acting barbiturate Baytenal (the sodium salt of 5,5 allyl (2 methyl propyl) thiobarbituric acid) suggests that this type of agent is infinitely preferable to thiopentone sodium for this type of examination. Deep sedation with rapid recovery occurred consistently and this suggests that one might be able to reduce or abolish the figure of 30.8 per cent of patients who remember something of the examination, without lengthening the awakening time.

A short-acting relaxant of the competitive type might permit some degree of spontaneous respiration. Prestonal has been reported upon. The author has no experience of this drug but understands that it is probably not the answer to this problem. Certainly, a technique using spontaneous respiration but permitting immediate postoperative consciousness and an active cough reflex should be the aim.

Many workers use Cuirass type respirators on patients who appear to be poor risks. The difficulty of selecting the poor risks (from the cardiac irregularity standpoint) has been mentioned and the inefficiency of this type of respirator on those with a fixed thoracic cage is well known.

Contraindications

Many anaesthetists believe that there are few contraindications to general anaesthesia. Certainly, as it exists today, it is unsuitable for those with myocardial ischaemia, gross anaemia, and empyemata with bronchopleural fistulae. Decompensated heart disease and orthopnoea are further contraindications. Pregnancy is a possible contraindication.

Although three epileptics were given local anaesthesia in this series, without mishap, it is thought that these and the one psychiatric case included should have had general anaesthesia.

One would conclude by saying that local anaesthesia is contraindicated for the patient who desires to be asleep and who has good cardio-respiratory function.

Summary

Some of the advantages and disadvantages of local and general anaesthesia for bronchoscopy have been discussed and the findings in a series of 275 cases reported. It is shown that general anaesthesia is preferable to a high percentage of patients, permitting an easier instrumentation and quicker examination and giving fewer complications of trauma; but the present technique, using succinylcholine and thiopentone, introduces several further complications, figures for which are given. It is suggested that, while each case should be considered on

its merits, general anaesthesia will be the anaesthesia of choice in the vast majority of cases. Suggestions are made for improvements in the current technique.

ACKNOWLEDGEMENTS

I should like to express my thanks to the various members of the consultant and registrar staff of the Brompton Hospital who took an active interest in this problem and who assisted in the collection of data.

RÉSUMÉ

275 anesthésies pour bronchoscopie pour fin de diagnostic servent de matière pour comparer les avantages et les désavantages de l'anesthésie locale et de l'anesthésie générale.

Le problème est abordé comme suit:

1. Une misse au point des conditions anesthésiques idéales pour la bronchoscopie. Dans le détail, on a tenu compte des considérants suivants: (*a*) Les meilleures conditions d'opération: ce qui devrait être le but de chacun; (*b*) L'importance du risque pour le malade. (*c*) L'acceptation de l'anesthésie locale par le malade. 47 pour cent de ceux à on avait fait une anesthésie locale opteraient pour une générale s'ils devaient avoir une autre bronchoscopie; 0.8 pour cent de ceux à qui on a fait une générale préféreraient une anesthésie locale si la chose était à recommencer.

2. Un rapport et une appréciation du degré de succès ou du manque de succès obtenu dans la série présentée soit sous anesthésie locale soit sous anesthésie générale. Des groupes comparables de malades ont été soumis, les uns à l'anesthésie locale, les autres à l'anesthésie générale; l'instrumentation dans le premier groupe a été plus difficile. L'examen a été fait en moins de temps et avec moins de traumatisme sous anesthésis générale.

Dans le groupe de malades examinés sous anesthésie locale, on a qualifié les résultats de bons, passables ou mauvais; 87 pour cent des cas sont entrés dans les deux premières classifications, mais seulement 20 pour cent des résultats étaient parfaits.

On présente des statistiques sur les vomissements postopératoires, la céphalée, les douleurs musculaires, les irrégularités du pouls, etc.; en ce qui concerne ces complications, les statistiques montrent que l'anesthésie générale en entraîne davantage; certaines de ces complications sont étudiées plus particulièrement.

Chez tous les cas soumis à l'anesthésie générale, on a noté le temps écoulé depuis la fin de l'examen au moment où le malade pouvait répondre à son appel. Dans la grande majorité des cas, cet espace de temps a été inférieur à cinq minutes.

3. On a étudié les améliorations possibles de la technique habituelle avec l'anesthésie générale si l'on emploie la succinylcholine et le thiopentone. Les contrindications sont énumérées.

A tout considéré, nous sommes d'avis que, bien que chacun des malades doit être étudié et pose son problème, l'anesthésie générale sera choisie dans la plupart des cas. Les techniques actuelles ne sont toutefois pas parfaites.

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PULMONARY FUNCTION TESTS*

FERNAND GRÉGOIRE, F.R.C.P. (C), F.C.C.P.**

IN the past decade, a large number of physiological tests have been developed for the quantitative and qualitative evaluation of pulmonary function; these are as important to the practice of medicine as are tests of renal, hepatic or neuromuscular function. They don't supplant other diagnostic procedures and cannot take the place of an anatomic, bacteriological, and pathological diagnosis, but they indicate how disease has altered function. After all, this is the important matter for anaesthesists.

The primary function of the lung is the uptake of an adequate amount of oxygen and the elimination of the excess of carbon dioxide. This involves, however, a number of processes which we have classified for the sake of simplicity in four categories:

I. Ventilation.
II. Diffusion.
III. Capillary blood flow in the alveoli.
IV. Compliance and elasticity or the mechanics of breathing.

TABLE I

BASIC TESTS OF CARDIO-PULMONARY FUNCTION

Ventilation	Diffusion	Capillary Blood Flow	Mechanics of Breathing
Lung volume	Breathing	Right	Recording of
Total volume	1, Room air	heart	intra-oesophageal
Vital capacity	2, Low or high	catheterization	pressures
Functional residual cap.	O_2 mixtures	for pulmonary	simultaneously
Expiratory reserve	Min Vent./L.	artery pressure	with air flow
Residual cap/total vol. %	O_2 cons/cc/min.	at rest and	to determine
Mixing index	CO_2 prod/cc.	at exercise	the stiffness
Maximum breathing cap.	R.Q.	with	or the
Minute ventilation	*Arterial Blood*	determination	distensibility
O_2 consumption	CO_2 Content	of the cardiac	of the lungs
CO_2 produced	O_2 content	output	and thorax,
Respiratory quotient	O_2 cap.	according to	i.e. the
Dyspnoea index	Hb O_2 % Sat.	the Fick	mechanical
Single breath test	pCO_2	principle	compliance
Bronchospirometry	pO_2		
Right % Left %	pH		
Min. vent.	Alv pO_2		
O_2 prod.	A.A. Grad.		
CO_2 prod.	% Venous admixture		
R.Q.	Capacity of diffusion		
V.C.	% Dead space		

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, Mont Tremblant, P.Q., June 18-20, 1956.

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A great number of tests have been developed in each category because no single one yields all the information desired, in any single patient. As a matter of fact, dyspnoea may result from ventilation insufficiency as judged by the first series with or without involvement of the other processes. On the other hand, the ventilatory reserves may be normal, but the patient cyanotic and much dyspnoeic if the diffusing capacity for oxygen is considerably reduced by an increased thickness of the alveolar membrane, as will be illustrated by the last case.

I. The *ventilation* must be adequate to maintain an alveolar pO_2 around 100 mm.Hg and an alveolar pCO_2 around 40 mm.Hg. What counts, then, is the alveolar ventilation. It is dependent on a great number of factors of which the most important are: (1) The tidal air; (2) The frequency of breathing; (3) The dead space; (4) The functional residual air. As a matter of fact the alveolar ventilation per minute is obtained by subtracting the dead space from the tidal air and multiplying by the respiratory rate.

$$\text{Alv. Vent.} = (\text{T.A.} - \text{D.S.}) \times \text{R.R.}$$

At rest, the tidal air is around 500 cc. and the dead space 150 cc. for normal men. The dead space should not make more than 30 per cent of the tidal air. For a given minute ventilation, when the D.S. is greater, the alveolar ventilation is smaller.

On the other hand, the dead space and the minute ventilation being constant, the respiratory rate is faster and the alveolar ventilation lower. Let us assume a tidal air of 150 cc. equal to the D.S. with a respiratory rate of 50/min. The total ventilation would be 7.5 l. per min., but the alveolar ventilation almost nil.

There will be a rapid drop of pO_2 and rise of pCO_2 with respiratory acidosis. On the other hand a tidal air of 1500 cc. with a respiratory rate of only 5 per minute, and the same dead space, will maintain the same total ventilation, but increase the alveolar ventilation to 6.75 l. per min., that is, more than sufficient to adequately ventilate the alveoli. The effect of the dead space in this case will be diminished to 10 per cent.

From the ventilatory point of view it is better to increase the depth of the respiration instead of the rate especially when the dead space is enlarged.

An increase in the functional residual capacity minimizes the effect of the tidal air and increases the time required to wash the alveoli. The tidal air being equal, it may take 12 instead of 6 breaths to renew the alveolar air.

The dead space is increased in absolute figures when the ventilation/capillary blood flow ratio is increased. In other words when the air goes in non-circulated alveoli, this air does not take part in exchanges and increases the total dead space.

It is evident that an increased dead space is a cause of hyperventilation.

On the other hand the minute ventilation and the maximum breathing capacity have a great influence on the apparition of dyspnoea because the shortness of breath usually starts when the ventilation reaches 30 per cent of the maximum breathing capacity.

II. In certain cases, the alveolar ventilation is adequate but the blood leaving the pulmonary capillaries may be only partly oxygenated if there is an impairment of the diffusion of O_2 through the alveolar membrane. We call this trouble a pulmonary capillary block and its importance is measured by the diminution of the diffusing capacity. This may be estimated by the CO method, the fastest and simplest, or by oxygen mixture breathing—the method that we actually use. It involves a complete study of alveolar ventilation and arterial blood.

The causes of diminution of the diffusing capacity may be classified as follows: (1) Diminution of surface area for diffusion by a sufficient decrease in the number of potent capillaries. (2) Distance for diffusion—any disease of the cardiopulmonary system which leads to intra-alveolar or interstitial pulmonary oedema or a thickening of the alveolar capillary membranes as found in pulmonary fibrosis, in vascular sclerosis, or in pulmonary oedema may decrease the diffusing capacity. (3) The qualities of the tissues. A fibrotic tissue may create more impairment of the O_2 diffusion than an oedematous tissue of the same thickness.

III. On the other hand, the normal pulmonary capillary blood flow is around five litres a minute at rest with a mean pulmonary artery pressure of 13 to 15 mm.Hg. that should not rise at exercise despite a great increase of the cardiac output. In many chronic pulmonary diseases, the pulmonary artery pressure is normal or higher than normal at rest and increases significantly at exercise.

The main causes of pulmonary hypertension are: (1) anoxia; (2) The consequent polycythemia and hypervolemia; (3) Increased cardiac output; (4) Reduction in capacity of pulmonary vascular bed.

The right heart catheterization gives us an objective idea of the pulmonary haemodynamics and is absolutely necessary in certain cases to fully appreciate the circulatory disturbances due to cardiopulmonary diseases.

IV. Finally the work of arterializing the venous blood should be achieved with a minimal expenditure of energy by the respiratory and circulatory systems.

The work of ventilating the lungs is done normally by the muscles of respiration. This muscular action is opposed by certain forces which may be divided in three components: (1) The force to overcome elastic resistance; (2) The force to move non-elastic tissues; (3) The force to overcome resistance to airflow through the tracheobronchial tree. Numerous tests are now available which measure the specific resistances to breathing and the forces required to overcome them. It would be too long to discuss these methods here, but we can say that they aid in more precise diagnosis and often in more specific therapy.

Now I would like to illustrate how advanced obstructive pulmonary emphysema, anaesthesia during thoracic surgery and pulmonary fibrosis, altered the respiratory function.

Table II illustrates the great diminution of the maximum breathing capacity and vital capacity with a considerable increase of the residual capacity in 25 emphysematous patients in the IVth stage. Table III includes the arterial blood studies on the same patients. The CO_2 content and pCO_2 are increased, the pH is down towards acidosis, and the saturation is around 80 instead of 95 per cent. The dead space is greatly enlarged and the diffusing capacity markedly reduced

TABLE II

PULMONARY EMPHYSEMA IV
(25 cases, Mean age 47)

MAXIMUM BREATHING CAPACITY			
	Determined	After vapo	Predicted
	30. L.	40 L.	141 L.

LUNG VOLUME	Determined	Predicted
Total capacity	5.95 L.	4.79 L.
Vital capacity available	2.14 L.	3.65 L.
Functional residual capacity	4.56 L.	1.79 L.
Expiratory reserve	.75 L.	.65 L.
Residual capacity	3.81 L.	1.14 L.
Resid. cap./Total cap. %	64. %	23.8 %
Mixing Index	7.1 %	1 to 2.5%

TABLE III

ARTERIAL BLOOD STUDIES AT REST

PULMONARY EMPHYSEMA	Determined	Predicted
Minute/ventilation in L./m^2 of body area	5.23	4
O^2 consumed in cc./min/m^2 of body area	144	130
R.Q.	.78	.80
CO^2 content vol. %	57.9	50.0
Saturation %	85	95
Arterial pO_2 mm.Hg.	57	88
Arterial pCO_2 mm.Hg.	54	40
Arterial pH	7.38	7.40
Alveolar pO_2 mm.Hg.	82	100
A.A. gradient in mm.Hg.	26	$<$ 12
D.S. in c.c.	228	160
D.S. in percentage of tidal air	45	$<$ 30%
Venous admixture in percentage of cardiac output	30	$<$ 6%
Mean capillary pressure for O_2	25	$<$ 20
Oxygen diffusion capacity/m^2 of body area	5.71	$>$ 8

at rest. It is evident that none of the subjects included in this study could afford a major thoracic operation.

Figure 1 summarizes the ventilation and acid base equilibrium studies of 23 non-emphysematous patients during major thoracic surgery. There was a significant diminution of alveolar ventilation with disturbances of ventilation/blood flow ratio, and a subsequent increase in pCO_2 content and respiratory acidosis. The breathing of enriched O_2 mixtures kept their blood fully saturated. As they were not emphysematous, they were able to hyperventilate and eliminate the excess of CO_2 in the first hours of recovery.

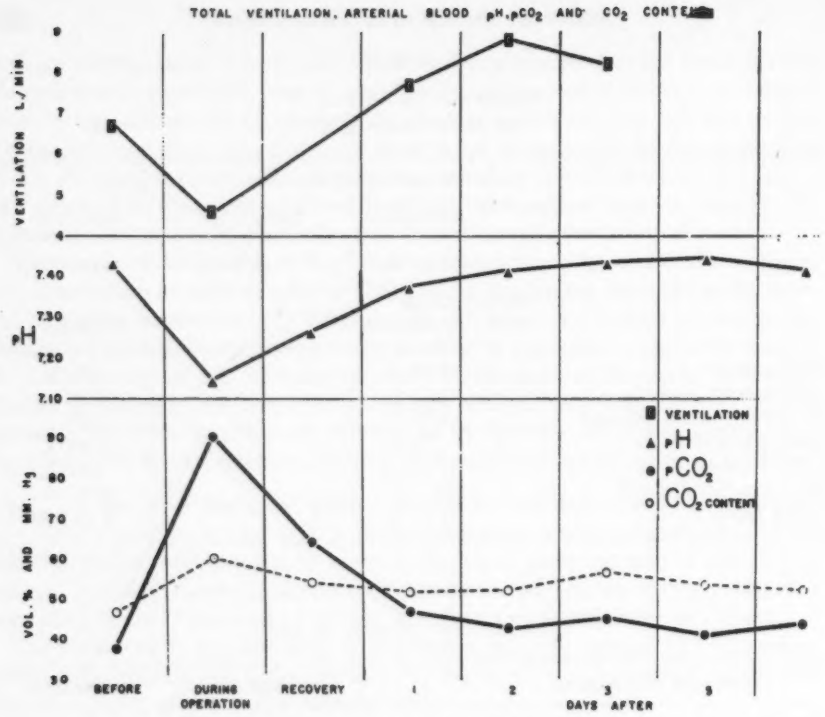

FIGURE 1. Acid base equilibrium during anesthesia.

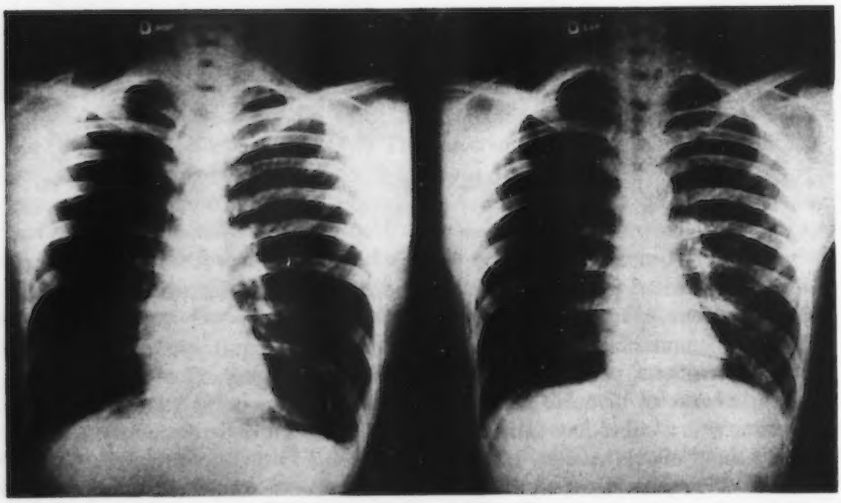

FIGURE 2. Inspiratory and expiratory X-ray (J.-G. A.)

Figure 2 represents the inspiratory and expiratory X-ray of a patient (Mr. J.-G.A.) 26 years old sent to us for cough and exertional dyspnoea. This man worked for many years in a dusty place and had suffered from chronic bronchitis since his childhood. For the last year he complained of dyspnoea at work. The X-rays show hypertransparence and trapping of air on the right side. The maximum breathing capacity is greatly diminished but the lung volume is not significantly altered, as seen in Table IV. The bronchospirometry is very instructive because it shows a great diminution of the function on the right side with an increased ventilation/blood flow ratio. At rest, the arterial blood is not normally saturated due to poorly ventilated areas in which the circulation is not proportionally diminished. The venous admixture is increased to 28 instead of 6 per cent. The diffusing capacity at rest is still in normal limits.

It is evident that this patient could be operated on in the right lung, but in case of a left lung tumor, the low function on the right would prevent a left pneumonectomy. It is very rare to find unilateral pulmonary emphysema and this patient is a good example of it.

The next patient (Mr. H.R.) is a 53-year-old male, referred to us for diagnosis and treatment of pulmonary fibrosis. The patient had noticed an increasing dyspnoea since 1947. He coughed and raised much whitish material but did not have fever and did not lose weight. He appeared hyperpnoeic, cyanotic and

TABLE IV

A Case of Unilateral Emphysema (Mr. J.-G. A.)

	Determined	Predicted
MAXIMUM BREATHING CAPACITY		
	66.55 L.	181 L.
LUNG VOLUME		
Total capacity	5.94 L.	5.79 L.
Vital capacity available	4.14 L.	4.64 L.
Functional residual capacity	2.95 L.	2.09 L.
Expiratory reserve	1.15 L.	.95 L.
Residual capacity	1.80 L.	1.15 L.
Resid. cap./Total cap. %	30.3 %	19.9 %

	Right Lung	Left Lung
BRONCHOSPIROMETRY		
Ventilation %	28.0	72.0
O_2 consumed %	21.7	78.3
CO_2 produced %	18.7	81.3
R.Q.	.63	.76
Vital capacity	34.9	65.1

TABLE V

A Case of Unilateral Emphysema (Mr. J.-G. A.)

Arterial Blood Studies	At rest		At exercise
	20.93% O_2	15.26% O_2	
Minute/ventilation in L.	9.06	8.80	29.1
O_2 consumed in c.c. per min.	267.	220.	966.
CO_2 produced in c.c. per min.	218.	210.	808.
R.Q.	.81	.96	.84
Dyspnea Index	33.9	40.	30.1
CO_2 content vol. %	48.67	48.43	46.61
O_2 content vol. %	16.71	15.95	17.94
O_2 capacity vol. %	18.22	18.29	19.16
Saturation %	91.7	87.2	93.6
Arterial pO_2 mm.Hg.	66.	57.	69.
Arterial pCO_2 mm.Hg.	46.	43.	40.
Arterial pH	7.36	7.39	7.42
Alveolar pO_2 in mm.Hg.	91.	63.	100.
A.A. Gradient in mm.Hg.	25.	6.	31.
D. S./T. A. %	42.9	39.5	36.6
Diffusion capacity		9.3	
Venous admixture %		28.	

had clubbing of the fingers. There were numerous dry rales at the bottom of both lungs. As can be seen from Table VI, the maximum breathing capacity is normal. This again emphasizes the impossibility of using it as single test. The lung volume is much smaller than normal and all the subdivisions are diminished. The arterial blood is slightly unsaturated at rest with an increased A.A. gradient and percentage of dead space, a diminution of the diffusing capacity at rest and

TABLE VI

A Case of Pulmonary Adenomatosis (Mr. H. R.)

Maximum breathing capacity	Determined	Predicted
	140.5	132 L.

Lung volume	Determined	Predicted
Total capacity	3.75 L.	5.50 L.
Vital capacity available	3.11 L.	4.16 L.
Functional residual capacity	1.38 L.	2.08 L.
Expiratory reserve	.74 L.	.73 L.
Residual capacity	.64 L.	1.34 L.
Resid. cap./Total cap. %	17.1 %	24.4 %

TABLE VII

A CASE OF PULMONARY ADENOMATOSIS (Mr. H. R.)

ARTERIAL BLOOD STUDIES AT REST	20.93% O_2	13.16% O_2
Minute/ventilation in L.	9.39	18.1
O_2 consumed in cc. per min.	260.	303.
CO_2 produced in cc. per min.	186.	303.
R.Q.	.715	1.
Dyspnoea index	36.	59.7
CO_2 content vol. %	52.65	46.26
O_2 content vol. %	15.77	12.55
O_2 capacity vol. %	18.36	20.95
Saturation %	85.9	60.
Arterial pO_2 mm.Hg.	54.	31.
Arterial pCO_2 mm.Hg.	37.	36.
Arterial pH	7.47	7.45
Alveolar pO_2 in mm.Hg.	97.	58.
A.A. gradient in mm.Hg.	43.	27.
D. S./T. A. %	46.	52.
Diffusion capacity		6.87
Venous admixture %		49.

a terrific increase of the venous admixture. Figure 3 provides an X-ray result for this patient.

A lung biopsy was done and there proved to be pulmonary adenomatosis. In this case an alveolar capillary block was responsible for the arterial unsaturation and the marked dyspnoea.

A general ideal of cardiopulmonary tests has been given. The importance of

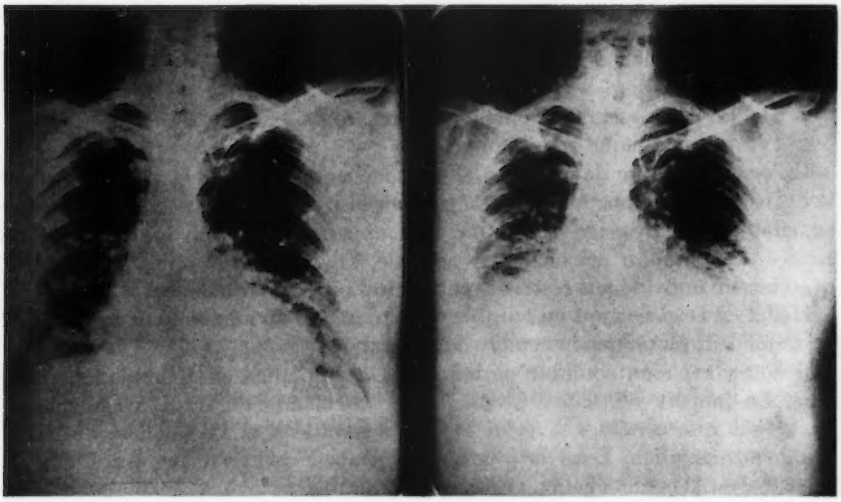

FIGURE 3. Inspiratory and expiratory X-ray (H. R.)

a physiological study has been stressed, for patients who suffer from a chronic cardiopulmonary condition, and who need major operation, especially on the thorax.

The data on different patients at rest during exercise and during anaesthesia have been presented to illustrate a few theoretical points of interest.

Conclusion

Comroe and his associates in their very instructive and concise book on clinical physiology, entitled *The Lung*, said: "Tests of pulmonary function have proved of definite value both in diagnosis and in guiding therapy of patients with cardiopulmonary disorders." I am sure that a larger utilization of these tests before operating on cardiopulmonary patients would give anaesthetists a better knowledge of the limitations and of the specific function that has been impaired and would help in the patient's pre- and postoperative care as much as in the choice of the anaesthetic.

Acknowledgments

I wish to thank Dr. Maurice Comeau, F.R.C.P.(C.) for the clinical studies on the cases presented and Dr. M. J. Laberge, Dr. Charles Lépine, R. Soucey, Ph.D., J. Lapalme, M.Sc. for the physiological studies.

Résumé

Durant la dernière décade, un grand nombre de tests physiologiques ont été développés pour l'appréciation qualitative et quantitative de la fonction pulmonaire, et sont demeurés aussi importants pour la pratique de la médecine que les tests de fonction rénale, hépatique ou neuro-vasculaire. On peut diviser la fonction respiratoire en quatre:

I. La ventilation
II. La diffusion
III. Le débit sanguin capillaire pulmonaire.
IV. La mécanique respiratoire.

Un certain nombre de tests sont affectés à chaque catégorie et aident à évaluer le degré d'atteinte fonctionnelle et à préciser sa pathogénie. Il ne faut pas oublier en effet que la dyspnée peut aussi bien apparaitre chez un individu dont la capacité respiratoire maximale est normale, s'il y a des troubles de diffusion, que chez un individu aux réserves ventilatoires fortement diminuées.

L'effet de l'espace mort ou nuisible doit être réduit au minimum en augmentant la profondeur plutôt que le nombre de respirations.

Il doit y avoir un équilibre parfait entre la ventilation et la circulation alvéolaire. Le rapport ventilation alvéolaire sur circulation est de 8. S'il augmente, c'est signe que certaines alvéoles sont hyperventilées, et s'il diminue c'est qu'il y a hypoventilation. Dans le premier cas, l'espace mort est augmenté, dans le second, c'est la contamination veineuse qui s'accroît.

Le travail d'oxygénation du sang veineux doit se faire avec un minimum de dépenses d'énergie par les systèmes circulatoires et ventilatoires. Le cathétérisme

cardiaque au repos et à l'effort apportera des précisions sur le débit cardiaque, les pressions dans l'artère pulmonaire et le travail du ventricule droit.

D'autre part des tests d'élasticité pulmonaire et de changement de volume par variation de pression, renseigneront sur le mécanique ventilatoire.

Pour terminer, quelques données physiologiques concernant des emphysémateux au dernier stade, des patients sous anesthésie et un cas d'adénomatose pulmonaire, ont été présentées afin d'illustrer quelques points importants.

Une plus grande utilisation de ces tests par les anesthésistes fournirait une meilleure connaissance du patient avant l'opération et une meilleure thérapeutique tant préventive que curative.

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NEWS LETTER

Annual Meeting, Canadian Anaesthetists' Society, 1956

The Annual Meeting was held at Mont Tremblant Lodge, Mont Tremblant, Quebec, June 18, 19, 20 with the Quebec Division acting as host. The weather and accommodation were delightful, and a spirit of *joie de vivre* prevailed amongst the 225 registered persons. This registration included 123 doctors, various members of families, and exhibitors.

The Scientific sessions were well attended, and the viewing of exhibits was facilitated by having them all in the same hall. The majority of papers dealt with clinical trials of new drugs, Dolitrone, Viadril, Pacatal, Ethyl Vinyl Ether, Fluoromar, Prestonal, Neraval. Other papers dealt with didactic subjects, anaesthetic techniques, and hypothermia. A very interesting film on a heart lung machine was shown, from Laval University. From the programme, it appears that Canadian Anaesthesia is practically all clinical, with little or no laboratory research in progress.

Two round table discussions were held, one on Anaesthesia for Caesarean Section, and the second, at the close of the meeting, on questions arising from preceding papers. These discussions were lively and provoked much comment from the audience. In contrast to the round table discussions, when the participants were brief and to the point, the majority of other papers exceeded the time limit, allowing little or no question period. It is suggested that at future meetings the time limit be strictly adhered to. It is also suggested that all papers be submitted prior to the meeting, so that there may be time for correction or rejection if necessary and for the Chairman of the session to have a copy to enable him to organize the discussion period.

Dr. Ralph Tovell, of Hartford, Connecticut, was the guest speaker at the annual dinner; Dr. Alan Noble, immediate Past President, displayed bilingual prowess, and introduced the President for 1956-57, Dr. Mel Bowering, Regina, Sask.

At the Annual General Meeting, the following points of interest arose:

1. There are 703 members in the C.A.S. of whom 429 are certified anaesthetists, and 26 are in countries other than Canada.

2. The *C.A.S. Journal* has a quarterly circulation of 1200, and copies are sent to 26 countries outside of Canada.

3. The C.A.S. has invited the World Federation of Societies of Anaesthesiologists to hold their next meeting in Canada, in 1960. If the invitation is accepted, tentatively the Meeting is to be held in Toronto, with Montreal as an alternative.

4. The Annual Meeting for 1957 will be held at the Bessborough Hotel, Saskatoon, Sask., June 24, 25, 26.

S. L. Vandewater

BOOK REVIEWS

OBSTETRICAL ANAESTHESIA, ITS PRINCIPLES AND PRACTICE. By BERT B. HERSHENSON, M.D. Springfield, Ill.: Charles C. Thomas; Toronto: Ryerson Press. Pp. 403. $10.50.

The title is somewhat misleading, as the text allots considerable space to anaesthetics in general, including a chapter on the signs of anaesthesia. The author has a tendency to be somewhat verbose, and in discussing such things as infant resuscitation, he includes just about every known method. The reviewer feels that this would confuse any reader, experienced anaesthetist or otherwise. There is a curious reference to local anaesthetics as "solid" anaesthetics, and spinal anaesthesia includes the intra- and extradural technique, with little said about the latter. In the chapter on relaxants, the doses suggested are no more than homeopathic, compared to the British and Canadian standard. The chapter on premedication on obstetrics is rather good with a complete review of the pharmacology of the drugs employed. The author in his preface states "Obstetrical Anaesthesia has been designed for the student of Medicine, the practicing physician, and the obstetrician in order to clarify the purposes of the anaesthesiologist."

S.L.V.

CONTROLLED HYPOTENSION. By DAVID M. LITTLE, Jr., M.D. Springfield, Ill.: Charles C. Thomas; Toronto: Ryerson Press. Pp. 159.

This short text is, in reality, a monograph on methods, physiological aspects, complications, indications, etc. of induced hypotension. It embodies a very extensive and excellent review of the literature, with over 500 references. Referred to throughout is the Yale University survey of induced hypotension, made in Great Britain and the United States, which revealed appalling figures on morbidity and mortality. The author points out the lack of fundamental investigation into the physiological changes, and shows how the indiscriminate use of induced hypotension increases the risk to the patient. It is a useful procedure in limited circumstances, as discussed under indications and requirements. This book is strongly recommended to all anaesthetists as it discusses from a clear, concise, and conservative viewpoint, a controversial subject.

S.L.V.

CLINICAL ANALGETICS. By E. G. GROSS, M.D. and M. J. SCHIFFRIN, PH.D. Springfield, Ill.: Charles C. Thomas; Toronto: Ryerson Press. 1955, $3.25.

This monograph in the American Lecture Series is well written and contains much interesting material. The introductory chapter states that it is intended for general practitioners, dentists, pharmacists, and medical students and it seems that it is well suited for such readers. It contains insufficient information for the

specialist anaesthetist and the emphasis is not arranged for such an audience.

Of the ninety pages of text, fourteen are spent on salicylates, paraminophenols, and pyrazolone and twenty on local anaesthetics. General anaesthetics are, by definition, not included.

The bibliographies, at the end of each section, are good.

H.B.F.

MYSTERIOUS WATERS TO GUARD. By WESLEY BOURNE, M.D., C.M., M.SC., F.R.C.P.(C), F.I.C.A., D.A., F.A.C.A., F.F.A.R.C.S. Toronto: Ryerson Press. Price $10.25.

This volume is a collection of papers previously published by Dr. Bourne. For those who appreciate the author's poetic prose and his command of the English vocabulary, it will be most pleasant reading, but even for those who appreciate nothing more than modern medical journalese the book presents an interesting panorama of the growth of knowledge of Anaesthesia from 1925 to 1952, as seen by one of the most widely known and best informed of Canadian anaesthetists. This reviewer felt that the Shelleyan adjectives and unusual verbs which "come at" one from every page were much better when coupled with Dr. Bourne's superb oratorical brilliance, but having heard the author speak on frequent occasions, he was able to imagine them issuing in golden tones rather than static in the cold printed page, and the whole experience was delightful. The addition of a sermon as the concluding essay in the volume rounds out the picture of the enigma that is Wesley Bourne, and I would recommend the volume particularly to those who know him and love him.

R.A.G.

COMPLICATIONS OF REGIONAL ANAESTHESIA. By DANIEL C. MOORE, M.D. Toronto: Ryerson Press. Price $11.50.

In this volume Dr. Moore presents a very complete discussion of the complications of regional anaesthesia in all its forms. The only fault which this reviewer finds with the volume is in the section relating to general toxic reactions to local anaesthetic drugs. Here the reference to a metallic taste as an indication of the commencement of a general toxic reaction is considered unfortunate, since this phenomenon occurs in every case in which Procaine is injected intravenously, without other evidence of toxicity. This reviewer is likewise unable to accept the point of view repeatedly expressed by Dr. Moore that depression of the central nervous system by local anaesthetic drugs is a direct result of previous overstimulation. These objections, however, in no way minimize the value of this volume, which should certainly be read by all anaesthetists who are doing regional anaesthesia. Dr. Moore is to be congratulated on the tremendous amount of effort which has gone into the preparation of this volume.

R.A.G.

CANADIAN ANAESTHETISTS' SOCIETY, NEW MEMBERS

THE following new members were approved by the Annual General Meeting of the Society at Mont Tremblant, Quebec, on June 20, 1956.

British Columbia

Dr. David Allen (O.M.)	92 Lonsdale Ave., N. Vancouver
Dr. Howard C. Carruthers (O.M.)	937 West 19th Ave., Vancouver
Dr. Gordon F. Clark (Cert)	1405 King's Avenue, West Vancouver
Dr. Donald Ralph Collins (O.M.)	Medical Clinic, Box 160, Powell River
Dr. George Frederick Day (Cert)	6649 Granville St., Vancouver
Dr. Gordon J. Fyffe (M.E.)	847 W. 67th Ave., Vancouver
Dr. John Harford Harland (M.E.)	834 Bennett, Lulu Island, Vancouver
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THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Editor
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VOLUME 3, 1956

Printed and Published for
THE CANADIAN ANAESTHETISTS' SOCIETY, Incorporated
516 Medical Arts Building, Toronto 5, Canada
by
University of Toronto Press
University of Toronto
Toronto 5, Ontario, Canada
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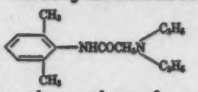

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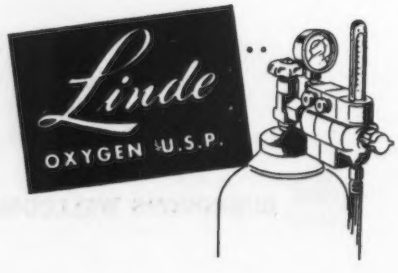

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The Society wishes to repurchase a limited number of copies of the January, April and July, 1955, and January 1956, issues of the Journal, at $1.00 per copy. Copies must be complete and unmarked, and should be forwarded to The Secretary, Canadian Anaesthetists' Society, 516, Medical Arts Building, Toronto 5, Ontario.

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